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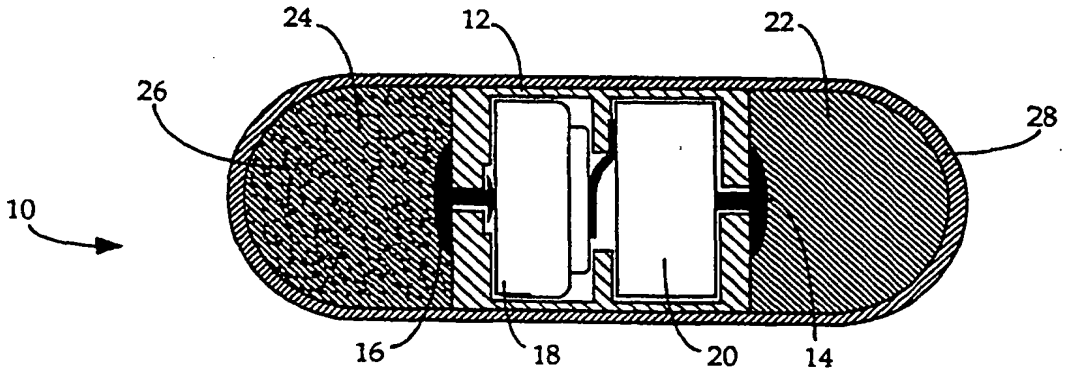

(57) Abstract

A system and method for enhancing the delivery of an agent (26), especially peptides and proteins, across the intestinal wall of a mammal. The system includes a device (10) for applying a potential across the intestinal wall so as to enhance delivery of the agent (26). The device (10) includes a pair of electrodes (14, 16) and a power source (18). An agent (26) may be located proximate to the intestinal wall separately from the device (10) or incorporated in the device (10). Electrical current is generated thereby enhancing delivery of the agent (26) across the intestinal wall. The agent and the electrode may be incorporated into a swellable polymer.

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Description

Method and system for enhancing delivery of an agent

Technical Field

This invention relates to a method and system for enhancing the delivery of an agent, and, in particular to devices and methods for use in enhancing delivery and delivering drug across the intestinal mucosa.

Background Art

The oral route of drug delivery is favoured for the delivery of drugs because the gastrointestinal tract is by its nature adapted to absorb nutrients ingested orally. It is also favoured over parenteral delivery routes for reasons of patient compliance, comfort and cost.

The simplest oral delivery mechanisms deliver the active ingredient to the stomach for moderate absorption due to low absorbing surface area. Controlled release formulations are designed to target release in specific areas of the gastrointestinal tract, or to sustain release for extended periods.

Proposals have been made to employ various types of oral drug delivery systems which employ electronic control means to release an active ingredient from a supply typically using a miniature pump inside a pill-like housing. Other devices use expandable compounds that osmotically force the active ingredient out in a controlled fashion.

Most drug substances are more readily absorbed in the intestine. Gastroretentive devices may assist in some fashion in the absorption of a particular drug because the device allows the drug to be released slowly from the stomach to the absorption site.

A disadvantage with these systems is that they can only deliver drugs in flowable form. Moreover, the nature of the drug which can be

delivered may be limited by interference by the mucose, acid pH, and enzymes of the stomach and intestines (as is the case with conventional or controlled release oral pharmaceutical formulations). In addition, the stomach is poorly adapted for absorption of drugs. One exception to this is aspirin, which is more soluble in acid in the stomach than in the intestine which has a higher pH.

Drug delivery experts continue to seek new and improved ways of delivering certain drugs orally or enhancing the oral delivery of drugs that normally have a poor uptake. Such drugs include macromolecules such as proteins and polypeptides which are subject to acid and enzyme attack and thus degradation in the gastrointestinal tract, particularly in the stomach, before being absorbed through the walls of the intestine for delivery to the bloodstream and ultimately their target site. Thus, peptides and polypeptides generally have very poor bioavailability when delivered orally due to instability and poor epithelial cell permeability.

Iontophoretic delivery is generally associated with delivery through the skin, where an entirely different set of conditions is encountered. The skin on the is a protective tissue which prevents unwanted substances from entering the underlying tissues. The skin has a number of layers, particularly the *stratum corneum*, requiring relatively high voltages for delivery. This may cause burns and irritation due to the high level of potential applied.

Thus, there is a need for a system and method that will safely and effectively enhance delivery of an agent across the intestinal wall.

There is a further need for a system and method that will enhance the delivery of peptides and proteins across the intestinal wall.

Disclosure of Invention

The present invention solves the problems associated with prior drug delivery and enhancement of drug delivery by providing a system

for enhancing delivery of an agent across the intestinal wall by applying potential across the intestinal wall.

The mucosal lining of the intestine is designed to absorb nutrients and their metabolites substances efficiently. Thus, it has been found that the application of low potential across the intestinal wall enhances the delivery of an agent across the wall. Unlike iontophoretic delivery via the skin, iontophoretic delivery *via* the intestinal mucosa as described herein is found to be a particularly efficient delivery route because the device can be activated when the agent reaches its most appropriate absorption window in the intestine, and enhance absorption of the agent across the intestinal wall.

The application of potential to the intestinal wall presents very little resistance to drug delivery. However, until now, no one has thought of applying potential to the intestinal wall to enhance drug delivery. Moreover, until now, no one has designed a system that may be ingested orally or delivered rectally to enhance drug delivery by applying potential across the intestinal wall.

Because the intestinal wall presents very little resistance to drug delivery, very low potential can be applied. Thus, the traditional problems associated with iontophoretic delivery via the skin, such as burns and irritation, do not arise in when iontophoretic delivery occurs in the intestine. The application of potential across the intestinal wall is not static when drug delivery is taking place due to peristalsis. However, because intestinal mucosal linings are more susceptible to damage than the cornified layer of the skin since the latter is exposed to the environment, it is particularly relevant that the application of a potential across the intestinal wall is not damaging to the intestinal mucosa. This is accomplished by showing reversibility of the effects of current on intestinal physiology.

It has been found that the application of a potential to the intestinal mucosa causes an increase in the uptake of active ingredient across the intestinal epithelium. This facilitates the delivery of

molecules which normally have a low uptake rate, particularly macromolecules such as proteins and polypeptides. However, the present invention can deliver peptides and other lower molecular weight active ingredients across the intestinal wall. It may also deliver non-polar cyclic oligopeptides such as the immunosuppressant cyclosporine and peptidomimetics.

In particular, the application of low potential to the intestinal mucosa in accordance with the invention increases the permeability of the tight junctions between the epithelial cells defining the epithelial cell monolayer of the gastrointestinal tract so as to result in increased transport of active ingredient from the lumen of the gastrointestinal tract to the bloodstream.

Generally described, a first embodiment of the invention provides a means for applying potential across the intestinal wall. The application means preferably comprises a pair of electrodes and a power source. A second embodiment of the invention may further include a means for locating an agent proximate to the intestinal wall. It is envisioned that the application of potential across the intestinal wall may enhance an agent already located proximate to the intestinal wall, or it may enhance the delivery of an agent incorporated within the system.

The application means may be ingested orally or delivered rectally.

It is preferred that the electrodes are in contact with the intestinal mucosa.

Preferably, the means for locating the agent proximate to the intestinal wall is actuated by a substance found within the gastrointestinal tract.

For example, the locating means can be actuated by the presence of the fluids of the gastrointestinal tract (or any aqueous solution).

Preferably, the locating means is covered by a pH-sensitive coating adapted to delay the actuation of the locating means until after the device has left the stomach and entered the small intestine.

Such pH-sensitive coatings are well known to those skilled in the art and are widely used in the manufacture of delayed release and controlled release tablets and capsules. The use of such coatings is particularly advantageous when the means for locatingthe electrodes and the intestinal mucosa proximate to one another is actuated by the presence of water in the gastrointestinal fluids. The pH-sensitive coating can protect the actuating means until the device has left the stomach and entered the small intestine, thereby effectively targeting the delivery of active ingredient to the correct site for absorption as the pH rises and strips the coating.

Further, preferably, the entire device is coated by a pH-sensitive coating which is insoluble in the environment of the stomach but which is soluble in the environment of the all regions of the intestine.

In alternative embodiments, the entire device is coated by a pH-sensitive coating which is impermeable in the environment of the stomach but which is permeable in the environment of the all intestinal areas beyond the stomach.

For example, it is possible to disperse particles of a polymer, the solubility of which is pH-dependent, throughout an insoluble coating. When the device reaches the small intestine, the soluble particles dissolve leaving a porous coating.

Polymer materials conventionally used as enteric coatings or to achieve delayed release effects can be used to form the pH sensitive coating. Typically such enteric coating polymers have a solubility which is highly pH dependent, the polymers being insoluble in gastric acid, but dissolving at intestinal pH. The pH sensitive polymers will be insoluble and impermeable in acid but will begin to dissolve at pH values in the range 4.5 - 7.0. Polymers that are used in enteric coating

depend on the presence of ionisable carboxyl groups in their molecular structure for their pH sensitivity. A sufficient portion of these acid groups, typically about 10%, must be ionised for water solubility to be achieved.

Preferably, the pH-sensitive coating can be selected from a cellulose acetate trimellititate, hydroxypropyl-methylcellulose phthalate, polyvinyl acetate phthalate, cellulose acetate phthalate and polymers of acrylic acid and/or methacrylic acid and esters thereof and poly-lysine.

In the case of polymers of acrylic and/or methacrylic acid representative polymers are polymers sold under the Trade Mark EUDRAGIT L, EUDRAGIT S and EUDRAGIT E. These polymers are polymeric lacquer substances based on acrylates and/or methacrylates and are manufactured and marketed by Rohm Pharma GmbH. In the case of hydroxypropylmethylcellulose phthalates (HPMCPs) various grades can be used such as HPMCP 50 and HPMCP 55. Another suitable enteric polymer is that sold under the Trade Mark AQUATERIC.

An amount of coating corresponding typically to 8-10% of the device weight or about 12mg cm^{-2} can be used to achieve acid resistance and impermeability. The coating is carried out in a manner known to those skilled in the art.

Preferably, the locating means comprises a swellable polymer, such as a hydrogel, forming at least part of each electrode, the polymer being caused to swell upon contact with a liquid in the gastrointestinal tract, and thereby causing the electrodes to move proximate to the intestinal wall, and preferably contact the wall.

Again, the skilled person will be familiar with a wide range of polymers which swell under predetermined conditions. Most preferably, the polymer used is water-swellable and is covered by a pH-sensitive coating as outlined above.

Further, preferably, each of the electrodes comprise a swellable polymer, namely any polymer which is approved for use in humans and which is swellable on addition to water by virtue of its hydrophilicity.

For example, the polymers can have properties typical of bioadhesive polymers which bind to mucous membranes and thus are hydrophilic and with a high proportion of hydrogen bonding groups and carboxylic acid groups.

More generally, the polymers should be charged or be capable of being functionalised with charged groups.

In such cases the swellable polymer is preferably electrically conductive to ensure correct operation of the electrodes.

The polymer associated with the anode will typically be a cross-linked cationic biodegradable hydrogel such as a polyvinyl pyrrolidone or a polyethylene imine.

The polymer associated with the cathode will typically be a cross-linked anionic biodegradable hydrogel such as a polyacrylic acid and derivatives thereof. A suitable polyacrylic acid is a polyacrylic acid sold under the Trade Mark Carbopol which is a water soluble, high molecular weight polymer of acrylic acid cross-linked with allylsucrose or allyl ethers of pentaerythritol. Another such polymer is polycarbophil, a water insoluble polyacrylic acid cross-linked with divinylglycol (3,4-dihydroxy-1,5-hexadiene). This polymer forms particles which swell in water. Other suitable polymeric materials include co-polymers of acrylic acid such as co-polymers of acrylic acid with polyethylene glycol.

A polymer associated with the cathode would also suitably be alginic acid or a salt thereof, such as the sodium, potassium or calcium salts.

Other suitable anionic polymers include tragacanth, which is a naturally occurring gum consisting of a mixture of water insoluble and water soluble polysaccharides, carboxymethyl cellulose and salts thereof, such as the sodium salt, hydroxypropylmethyl cellulose, hyaluronic acid and esters thereof, such as the benzyl ester, chitosan, polyanhydride co-polymers of fumaric and sebacic acid and polyesters and polyanhydrides in general.

Alternatively, the swellable polymer can also be an inert polymer. Examples of suitable inert polymers include ethylcellulose, methylmethacrylate, ethylmethacrylate, polyethylene, polypropylene and polyvinyl chloride.

When delivery of active ingredient is completed, the polymers are either degraded in the colon and/or expelled together with the miniature power source.

The active ingredient can be uncharged, positively charged, negatively charged or a zwitterion.

In preferred embodiments, the active ingredient is dispersed in the polymer material of at least one of the electrodes.

In the case of a chargeable active ingredient, as current flows through such an electrode, the active ingredient is ionised and acts as a charge carrier to carry current into and through the intestinal wall. The choice of electrode assembly (i.e. cathode or anode) in which to disperse the drug depends on the polarity of the drug molecule.

When the active ingredient is uncharged it can be coated with a suitably charged material.

The term active ingredient as used herein includes such coated active ingredients.

As indicated above, the active ingredient is preferably a peptide, polypeptide or protein or other macromolecular species.

Typical active ingredients include hormones such as insulin, calcitonin, calcitonin gene regulating protein, atrial natriuretic protein, colony stimulating factor, betaseron, erythropoietin (EPO), interferons such as α, β or γ interferon, somatropin, somatotropin, somastostatin, insulin-like growth factor (somatomedins), luteinizing hormone releasing hormone (LHRH), tissue plasminogen activator (TPA), growth hormone releasing hormone (GHRH), thyrotropin releasing hormone (TRH), oxytocin, estradiol, growth hormones, leuprolide acetate, factor VIII, interleukins such as interleukin-2, and analogues thereof and immunosuppressants such as cyclosporines. Oral delivery of vaccines may also be included because the delivery system may act as an adjuvant due to temporary inflammation of the intestinal epithelia, an action to which at least part of typical adjuvant effects are attributed.

However, typically the active ingredient will be any active ingredient which is normally administered by the parenteral route because it is not suitable for conventional oral delivery, including controlled absorption.

The electrodes may be made typically of Ag/AgCl, platinum, stainless steel or carbon.

The current can be DC, in which case the active ingredient will be delivered from the polymer associated with one electrode only, the other electrode serving as a counter-electrode.

Alternatively, the current flow can be intermittent or pulsed. When the current flow is intermittent, the active ingredient can be delivered successively from polymers associated with each of the electrodes.

The current will flow once the circuit is completed. The potential applied across the intestinal wall is in the range of between 0.5 and 6

volts, with a preferred range of between 10 and 60mV. Higher voltages can also be used, if required.

The device will preferably include a conventional microprocessor powered by a solid state miniature battery, especially a polymer-based solid state miniature battery. The microprocessor can be pre-programmed to control the rate of delivery of active ingredient, if required.

The device according to the invention can include one or more sensors for sensing various conditions within the body and for controlling a microprocessor in response thereto. For example, the sensors may be or include any one or more of the following:

i) a biosensor sensitive to a biological parameter;

ii) a pH sensor to effect the delivery of the active ingredient (e.g. insulin);

iii) a temperature sensor to control the delivery of the active ingredient in response to the body temperature;

iv) a sound sensor (e.g. a microphone) to control the delivery of the active ingredient in response to the pulse rate; or

v) a moisture sensor responsive to moisture entering the device, for example when the pH resistant coating has been removed.

Suitably, the supply of active ingredient may comprise nanoparticles of a chargeable polymer in which the active ingredient is embedded or entrapped.

Thus, rather than embedding raw active ingredient as such in the polymer of the electrode, it would be possible and in many cases advantageous to firstly formulate the active ingredient in nanoparticles or microparticles and then provide a supply of these particles for

iontophoretic delivery. The nanoparticles or microparticles would be uniformly distributed throughout the polymer in a manner known by those skilled in the art.

Such a supply of active ingredient is particularly advantageous when the active ingredient is not readily chargeable and/or when the active ingredient is susceptible to extensive degradation in the gastrointestinal tract. The device according to the invention is thus particularly suitable for use in the delivery of peptides, polypeptides and proteins and vaccines.

As indicated above, the device according to the invention may further comprise an electronic controlling circuit for controlling the rate of delivery of the active ingredient from the device.

The present invention is further directed to a method of enhancing the delivery of an agent across the intestinal wall by applying potential across the intestinal wall. The step of applying potential across the intestinal wall may be accomplished by applying a pair of electrodes in electrical communication with a power source to the intestinal wall.

The method of enhancing delivery may further include the step of locating an agent proximate to the intestinal wall so that when potential is applied, delivery of the agent thereacross is enhanced. This step may be accomplished by incorporating the agent in a swellable polymer.

Other objects, features and advantages of the present invention will become apparent upon reading the following detailed description of the embodiments of the invention , when taken in conjunction with the drawings and appended claims.

Brief Description of Drawings

Fig. 1 is a schematic sectional side view of an orally administrable drug delivery device according to the invention, before use;

Fig. 2 is a sectional side view of the device of Fig. 1, shown immediately after it enters the small intestine;

Fig. 3 is a sectional side view of the device of Fig. 1 when delivering drug within the small intestine;

Fig. 4 is a sectional side view of the device of Fig. 1 when delivering drug within the small intestine and showing the direction of current flow;

Fig. 5 is a graph of Papp (cm/s) for ^{14}C-mannitol *v.* time interval (min.) across a control and test tissue as described in Example 1;

Fig. 6 is a graph of Papp (cm/s) xe-06 *v.* charge (μ-equivalents) for a control and test tissue as described in Example 1;

Fig. 7 is a graph of short-circuit current (μA) *v.* time (min.) and in response to forskolin for a control and test tissue as described in Example 1;

Fig. 8 is a graph of TEER (ohm.cm^2) *v.* time (min.) for a control and test tissue as described in Example 1;

Fig. 9 is a graph of charge transferred (μ-equivalents) *v.* time period (min.) for a control and test tissue as described in Example 1;

Fig. 10 is a graph of Papp (cm/s) for ^{14}C-mannitol *v.* time (min.) across a control and test Caco-2 cell monolayers as described in Example 2;

Fig. 11 is a graph of TEER (ohm.cm^2) *v.* time (min.) for a control and test Caco-2 cell monolayers as described in Example 2;

Fig. 12 is a graph of short-circuit current (μA) *v.* time (min.) for a control and Caco-2 cell monolayers as described in Example 2;

Fig. 13 is a graph of charge transferred (μ-equivalents) across epithelium *v.* time interval (min.) as described in Example 2;

Fig. 14 is an electron micrograph of a control Caco-2 monolayer (Magn. x 10,000) as described in Example 2;

Fig. 15 is an electron micrograph of a Caco-2 monolayer subjected to 9.4 μ-equivalents charge (Magn. x 7,000) as described in Example 2;

Fig. 16 is a graph of Papp (cm/s) for TRH *v.* time interval (min.) across a control and test tissue as described in Example 3;

Fig. 17 is a graph of TEER (ohm.cm^2) *v.* time (min.) for a control and test tissue as described in Example 3;

Fig. 18 is a graph of short-circuit current (μ A) *v.* time (min.) and in response to forskolin for control and test tissue as described in Example 3; and

Fig. 19 is a graph of charge transferred (μ-equivalents) across epithelium *v.* time interval (min) as described in Example 3.

Modes for Carrying Out the Invention

Referring now in more detail to the drawing, in which numerals refer to like parts throughout the several views, Fig. 1 shows an orally administrable drug delivery device 10. The device 10 comprises a central housing 12 from which a pair of electrodes 14,16 extend. A battery 18 and microprocessor 20 are connected in series between the electrodes 14,16. When the circuit between the electrodes 14,16 is completed, as will be explained further below, the battery 18 drives a current through the circuit, the current being controlled by the microprocessor 20.

The electrodes 14,16 are each associated with a swellable polymer and define an anode 22 and a cathode 24, respectively. The cathode 24 has an active ingredient 26 uniformly distributed throughout an alginate polymeric material.

Because the alginate is an electrically conductive polymer it will be clear to the skilled person that the device 10 can form an iontophoretic drug delivery device when the circuit between the anode 22 and the cathode 24 is completed and the battery 18 is energised.

The device 10 is provided with a gastroresistant coating 28 of HPMCP, which is insoluble in the stomach and soluble in the intestinal tract due to the pH-dependent solubility which it exhibits. Thus, the coating 28 remains intact after the device 10 is ingested until the device 10 passes from the stomach to the small intestine. The dissolution of the coating 28 occurs when the device 10 enters the small intestine is represented schematically in Fig. 2.

When the coating 28 dissolves, the anode 22 and the cathode 24 are exposed to the juices in the small intestine. Because the alginate is

not only conductive but also swells when exposed to water, the dissolution of the coating 28 allows the anode 22 and the cathode 24 to swell as shown in Fig. 3. Due to the size of the intestinal tract and the size of the anode and cathode, after swelling the anode and cathode are able to locate themselves proximate to or in contact with the mucosa of the intestine. The proximate location of the electrodes to the mucosa or the direct contact completes the electrical circuit between the anode 22 and the cathode 24 and enables drug to be delivered via iontophoresis.

The direction of current flow is depicted in Fig. 4.

The microprocessor 20 incorporates a leakage current sensor which senses when the circuit between the anode 22 and the cathode 24 is completed and actuates a switch accordingly to energise the battery 18. The battery 18 drives a current between the anode 22 and the cathode 24, to thereby drive the active ingredient 26 in the cathode 24 through the epithelial layer of the small intestine.

The microprocessor 20 also incorporates a current control circuit (not shown) which maintains a constant current through the circuit in order to maintain a constant delivery rate (thereby compensating for any variations in circuit resistance as the device 10 passes through the small intestine). More sophisticated controlling circuitry may be incorporated as desired, e.g. to vary the delivery rate or to switch off delivery after a predetermined time or a predetermined amount of delivery of active ingredient.

Unlike the skin, the intestinal walls 30 are adapted to readily absorb molecules and ions, so iontophoretic delivery according to the present invention is advantageous because a much lower delivery current is required due to the lower transepithelial resistance of 40-80 ohms - cm^2.

Furthermore, the active ingredient is delivered directly to the circulatory system, rather than to the subcutaneous region where the active ingredient may build up in amounts which inhibit further

absorption or which limit the rate at which the drug passes into the bloodstream (the so-called "depot effect").

A further advantage of the present invention is the avoidance of burns along the intestinal tract. Because the device 10 is swept along the intestinal tract naturally, the problems of burning due to electrical currents passing through an area over extended periods of time are naturally avoided. Any individual area of the intestinal wall is only subjected to electrical current for a short period of time.

The description above is directed to the construction and operation of the device. We now turn to a series of experimental examples demonstrating the successful operation of the methodology that would be employed in the in vitro and the successful transport of drug across the intestinal mucosa applying such methodology.

Example 1

Use of iontophoresis to increase the transport of ^{14}C-mannitol across rat colonic tissue in vitro

An in vitro experiment was carried out to assess the permeability of rat intestinal tissue mounted in Ussing chambers using current of the type employed in the device according to the invention. The rats used were Wistar rats. The experimental model used comprised five periods: two basal periods and two recovery periods, each 20 min. in duration, separated by a stimulatory test period also 20 min. in duration. The colonic rat mucosal segment (area 0-63cm^2) was not voltage/current clamped during the basal and recovery periods i.e. open circuit. However, during the test period the tissue in the diffusion chamber was current clamped and a current was applied that would transfer the desired charge (μ-equivalents) across the tissue. In the following set of experiments the following levels of charge were examined: 6.8 μ-equivalents (550μA x 20 min.), 9.4 μ-equivalents (750μA x min.), 11.9μ -equivalents (950μA x 20 min.), 14.3μ -equivalents (1150μA x 20 min. = 766 x 30 min.) while the control was zero. Ag/AgCl electrodes were

used to pass and monitor current using a DVC 1000 voltage clamp apparatus (WPI).

The paracellular flux marker ^{14}C-mannitol was used to indicate any absorptive flux enhancement across the intestinal tissue through epithelial tight junctions due to imposed current conditions. Samples were taken at 0, 20, 40, 60, 80 and 100 min. The permeability co-efficient (Papp) was measured for mannitol using the following equation

$$Papp = dc/dt.1/A.Co$$

where dc/dt= transport rate,mol/sec.

A=surface area of the membrane in cm^2

Co=initial concentration in donor chamber, mol/ml

Transepithelial electrical resistance (TEER) was measured at 0, 20, 40, 60, 80 and 100 min.

Short-circuit current (SCC) was measured at 0, 20, 40, 60, 80 and 100 min.

The capacity of the tissue to respond to application of the secretagogue, forskolin (3μM and 7μM), was used to confirm tissue viability at the end of each experiment.

RESULTS: The Papp values (cm/s) measured for mannitol for each sampling period are outlined in Table 1 and Fig. 5.

Table 1

Papp (cm/s) value calculated for each 20 minute interval

control (n=5)			6.8µ-equiv. (n=4)		
interval	mean	sem	interval	mean	sem
0-20	1.99E-06	4.65E-07	0-20	2.18E-06	8.89E-07
20-40	5.69E-06	1.16E-06	20-40	4.36E-06	1.70E-06
Test	8.47E-06	141E-06	Test	8.76E-06	1.21E-06
60-80	6.96E-06	6.92E-07	60-80	6.74E-06	1.27E-06
80-100	5.56E-06	7.41E-07	80-100	2.27E-06	4.27E-07
9.4µ-equiv. (n=4)			11.9µ-equiv. (n=4)		
interval	mean	sem	interval	mean	sem
0-20	2.93E-06	1.10E-06	0-20	2.33E-06	1.24E-06
20-40	4.25E-06	1.12E-06	20-40	5.91E-06	1.12E-06
Test	1.01E-05	1.24E-06	Test	1.26E-05	1.78E-06
60-80	8.50E-06	6.23E-07	60-80	9.47E-06	1.52E-06
80-100	5.60E-06	1.49E-06	80-100	1.02E-05	2.49E-06
14.3µ-equiv. (n=4)					
interval	mean	sem			
0-20	3.01E-06	8.43E-07			
20-40	6.37E-06	1.26E-06			
Test	1.32E-05	9.36E-07			
60-80	9.77E-06	2.18E-06			
80-100	5.61E-06	1.36E-06			

The second basal period was used as the control to compare against the test period because of the lag in the mannitol flux seen in the initial 20 min. flux. It will be observed that for the control experiments

the mannitol flux was linear across rat colon throughout the remainder of the experiment. A similar trend was seen for the 6.8μ-equivalent test experiments. Following the 9.4, 11.9 and 14.3μ-equivalent experiments, mannitol flux was statistically enhanced across the epithelial tissue when compared with its own control period.

Of particular interest in the final 20 min. recovery period in all experiments, was the fact that the mannitol fluxes reverted to values similar to the unstimulated control for that period. This demonstrates reversibility of the effect and thus, that application of these current levels to the intestinal mucosa is not permanently damaging.

Closer analysis of the Papp values for the test period showed that the 14.3μ-equivalent test compared to the control flux was significantly enhancing the flux of mannitol. Furthermore, a plot of the relationship between charge (μ-equivalents) and Papp for the test data is plotted in Fig. 6 . It is clear that there is a direct linear relationship between the two (regression of line in Fig. 6 is equal to 0.96). As charge (Q/F), where Q=charge in Coulombs, is calculated by current (amps) x time (seconds)/Faraday's constant, it is clear that there is a direct proportional link between charge transfer and Papp, the permeability co-efficient. In other words, the flux of mannitol is related to the current imposed on the isolated colonic tissue.

Short-circuit current was stable throughout the experiments and importantly, the forskolin-stimulated short circuit current was within control parameters and hence verified tissue integrity as shown in Table 2 and Fig. 7. In intestinal tissue an increase in short circuit current in response to adenylate cyclase activation leads to eletrogenic chloride secretion without fail, unless the tissue is damaged by means of breakdown of the functional epithelium. Taken together, the reversible increase in mannitol flux and maintenance of the capacity to secrete chloride prove that imposition of the current did not damage the epithelium.

Table 2

Short-Circuit Current reading at t=0, 20, 40, 60, 80, 199 min. and response to 3 and 10 μM Forskolin

Expt:	Short-circuit current measured at:						FSK	
control (n=5)	t=0	t=20	t=40	t=60	t=80	t=100	3μM FSK	10μM FSK
mean	7.50	6.10	4.40	3.80	3.30	4.10	20-50	64.10
sem	1.70	0.83	0.24	0.44	0.80	0.68	1.12	9.38
6.8μ-equiv. (n=4)								
mean	5.38	4.50	5.13	5.25	6.38	9.00	32.63	49.50
sem	1.91	1.79	2.68	4.21	3.80	2.58	9.91	10.63
9.4μ-equiv. (n=4)								
mean	10.88	8.50	7.13	5.38	5.25	6.00	16.25	41.63
sem	1.98	1.71	1.05	0.94	1.01	1.02	3.50	9.81
11.9μ-equiv. (n=4)								
mean	5.75	4.50	5.13	7.88	10.13	8.25	28.25	51.63
sem	1.36	1.44	1.77	3.33	4.72	4.78	10.61	9.79
14.3μ-equiv. (n=4)								
mean	7.13	3.48	4.00	4.50	7.00	10.50	32.38	45.00
sem	2.66	1.20	1.37	1.59	1.62	2.12	3.84	6.27

Although the transepithelial resistance (TEER) dropped during the initial stages of the experiments as shown in Table 3 and Fig. 8 the values were within the range in which the integrity of the colonic tissue tight junctions of the epithelium are maintained.

It is interesting to note that for the 14.3μ equivalent test tissue, a significant drop in resistance was observed at t=60 minutes. However, the resistance of the tissue returned to within normal levels during the recovery period. This demonstrates again the reversibility of the effects of the imposed current.

The charge equivalent being transferred across the epithelium was calculated for each experiment as shown in Table 4 and Fig. 9 to investigate the correlation between the mass or charge of a substance being transferred from one electrode to another and the Papp value of mannitol, previously shown in Fig. 6.

A correlation between flux of mannitol and charge transfer allows for the prediction of iontophoretic parameters.

Table 3

Transepithelial Resistance measured at t=0, 20, 40, 60, 70, 100 min.

Transepithelial Resistance (Ohm.cm^2) measured at t=0, 20, 40, 60, 80, 100						
Test voltage applied at T=40 min.						
Expt:						
control	t=0	t=20	t=40	t=60	t=80	t=100
mean	109.77	70.64	55.82	54.11	55.79	54.64
sem	14.55	13.06	7.18	10.33	7.87	6.94
6.8µ-equiv. (n=4)						
mean	103.54	72.76	47.65	35.35	42.51	46.83
sem	26.77	20.20	10.18	6.30	8.59	8.57
9.4µ-equiv. (n=4)						
mean	101.62	76.24	63.46	50.84	51.15	52.68
sem	12.91	9.97	7.80	6.46	6.53	6.10
11.9µ-equiv. (n=4)						
mean	68.67	43.89	33.40	24.23	22.44	22.90
sem	12.91	9.97	7.80	6.46	6.53	6.10
14.3µ-equiv. (n=4)						
mean	113.70	69.58	50.73	41.25	47.82	57.22
sem	19.13	12.29	8.19	6.97	9.95	12.93

Table 4

Charge (μ-equivalents) transferred across epithelium

Charge (μ-equivalents) transferred across epithelium calculated for each experiment					
Tissue under open circuit except for test period (*t=40-60)					
TEST:					
control (n=5)	t= 0-20	t=20-40	*t=40-60	t=60-80	t=80-100
mean	0.003	0.002	0.002	0.002	0.002
sem	0.001	0.001	0.001	0.001	0.001
6.8μ-equiv. (n=4)					
mean	0.002	0.002	6.859	0.002	0.003
sem	0.001	0.001	0.053	0.001	0.001
9.4μ-equiv. (n=4)					
mean	0.004	0.003	9.409	0.003	0.003
sem	0.000	0.000	0.021	0.001	0.000
11.9μ-equiv. (n=4)					
mean	0.004	0.004	11.949	0.005	0.003
sem	0.000	0.001	0.004	0.001	0.001
14.3μ-equiv. (n=4)					
mean	0.001	0.001	14.403	0.001	0.008
sem	0.001	0.001	0.051	0.001	0.003

The establishment of a charge-response curve has illustrated the minimum charge possible to cause a significant flux enhancement across the intestinal tissue segment which appears to be approximately 9μ-equivalents.

Example 2

Effect of Iontophoresis on the Permeability Mannitol across Caco-2 monolayers

This provides a useful contrast between the flux across a monolayer (Caco-2 cells) and the epithelium and attendant lamina propria (stripped colonic tissue of Wistar rats), as described in Example 1.

In this example, we used human intestinal monolayers of epithelia in a reductionist approach to testing the iontophoretic effect. Lamnia propria etc are absent so we can directly measure the effect of current on the key cells of the human gut.

A) Permeability experiments in Caco-2 cells:

Caco-2 cell monolayers were cultured in Dulbecco's Modified Eagles Medium (DMEM) 4.5 gL glucose supplemented with:

1% (v/v) non essential amino acids;

10% Foetal calf serum; and

1% penicillin/streptomycin

at 37°C and 5% CO_2 in 95% relative humidity. The cells were grown and expanded in normal tissue culture flasks and passaged once they attained 100% confluence. Caco-2 cells were seeded on Transwell (Transwell is a Trade Mark) filters (Costar, 6.5mm diameter, 0.4μM pore size) at a density of $5x10^5$ cells/cm^2 and incubated in 48 well

culture plates with a medium change every second day. Confluent monolayers between day 20 and day 30 post seeding on filters were routinely used for transepithelial transport studies within the laboratory. Days 28-30 were used for these experiments.

The experimental model consisted of five periods; two basal periods and two recovery periods each 20 min. in duration separated by a stimulatory test period also 20 min. in duration. The cells were not voltage/current clamped during the basal and recovery periods i.e. open circuit. During the test period, the cells were current clamped in a diffusion chamber and a 750μA current applied for 20 min. i.e. 9.4μ-equivalents of charge was transferred across the epithelial monolayer. The paracellular flux marker ^{14}C-mannitol was again used to indicate any absorptive flux enhancement due to the imposed current conditions.

The Papp values (cm/s) measured for mannitol for each sampling period are shown in Table 5 and Fig. 10.

Table 5

Papp (cm/s) value calculated for each interval in Caco-2 cells

Papp(cm/s) value for mannitol calculated for each interval					
Caco-2 cells: passage 28					
*Test voltage applied at 40-60 interval					
	control (n=3)			9.4μ equiv. (n=4)	
interval	mean	sem	interval	mean	sem
0-20	3.17E-07	1.24E-07	0-20	2.89E-07	2.43E-07
20-40	2.40E-07	1.29E-07	20-40	6.17E-07	2.71E-07
40-60	1.57E-07	3.09E-08	*40-60	5.34E-06	2.85E-07
60-80	1.99E-07	1.35E-07	60-80	1.43E-06	5.31E-07
80-100	3.61E-07	3.96E-07	80-100	6.49E-07	3.97E-07

Control values (n=3) were linear with time throughout the entire flux experiment. Following the application of the test current, the mannitol flux was enhanced approximately nine fold. Consequent to the termination of the applied current, the apparent permeability value decreased and resumed to within normal parameters. This finding was further supported by the transepithelial resistance (TEER) values which

were measured every 20 min. throughout the experiment as shown in Table 6 and Fig. 11.

Table 6

TEER measurements in Caco-2 cell monolayers

Transepithelial Resistance (Ohm.cm^2) measured at t=0,20,40,60,80,100 min.						
Test current applied at T=40 min.						
Expt:						
control (n=3)	t=0	t=20	t=40	t=60	t=80	t=100
mean	433.33	505.56	433.33	505.56	375.56	375.56
sem	0.00	72.22	0.00	72.22	57.78	57.78
9.4 µ-equiv. (n=4)						
mean	595.83	595.83	514.58	179.91	379.17	417.08
sem	54.17	54.17	81.25	5.80	31.27	85.47

It is clear that the application of the current is directly affecting the monolayer. In fact the applied charge causes the resistance value of the monolayer to fall by 65%. However, the resistance recovers within 40 min. of cessation of the applied current. Drop and recovery of

resistance is associated with tight junction opening in the test period followed by junction closure as the current was removed.

Short circuit was stable throughout all of the experiments as shown in Table 7 and Fig. 12.

Table 7

Short-circuit current readings in Caco-2 cell monolayers

Expt:	Short-circuit current measured at:					
control (n=3)	t=0	t=20	t=40	t=60	t=80	t=100
mean	2.33	2.50	2.50	2.17	2.33	2.00
sem	0.17	0.00	0.00	0.17	0.17	0.29
9.4 μ-equiv. (n=4)						
mean	1.75	1.50	1.63	1.13	1.50	1.75
sem	0.25	0.20	0.24	0.52	0.29	0.32

No forskolin (added at the end of the experiment to verify cell viability) stimulated increases in short-circuit current occurred; both control and test cells did not respond to 10μM forskolin. However, this is common in the case of Caco-2 cells.

The charge equivalents being transferred across the monolayer were calculated for each experiment and are set out in Table 8 and Fig. 13.

Table 8

Charge (μ-equivalents) transferred across Caco-2 monolayer

Charge (μ-equivalents) transferred across epithelium calculated for each experiment					
Tissue under open circuit except for test period (*40-60)					
TEST:					
control	t=0-20	t=20-40	t=40-60	t=60-80	t=80-100
mean	0.003	0.003	0.001	0.003	0.002
sem	0.001	0.001	0.000	0.001	0.001
9.4μ-equiv.					
mean	0.003	0.003	9.369	0.003	0.002
sem	0.000	0.000	0.057	0.000	0.001

B) Transmission Electron Microscopy:

Transmission electron microscopy (TEM) of both a control Caco-2 monolayer and that of a monolayer subjected to current (9.4μ-equivalents) were used to visualize any intracellular or cytotic effects. Cells were allowed to equilibrate for approximately 20 minutes in the diffusion chamber prior to the application of the current. On completion

of the iontophoretic test period, the cells were fixed in 3% glutaraldehyde.

Figs. 14 and 15 are electron micrographs of a control Caco-2 monolayer and a monolayer subjected to 9.4μ-equivalents charge, respectively. The test current was as used in the permeability experiments in part A) above.

Villi were normal in the control and test samples which indicates that there is no direct insult/toxic effect to the cell as a result of the applied current. Tight junctions can be visibly seen to have been dilated in the test specimen. The desmosomes too have been opened; the distinctive "kiss-sites" are not in contact.

The main point of interest from the test electron micrograph (Fig. 15) is the appearance of large vacuoles in the cytoplasm. These vacuoles appear organised and may be a consequence of the applied current. However, we have seen such vacuoles in electron micrographs from control cells on occasion

The cells in the test sample are widening in general but narrow towards the bottom of the basolateral side (not shown). This effect is quite common in treated cells.

Analysis of the TEMs supports the hypothesis that the iontophoresis is increasing the transport of test substances across the epithelial cells *via* the paracellular route. However, the large vacuoles present in the cytoplasm may suggest a transcellular contribution. The TEMs demonstrate that the applied current is not causing damage/toxic insult to the cells. The reversibility of the increased mannitol flux, maintenance of short-circuit current, reversible decrease in TEER and acceptability of the EM photographs of the cells all suggest that iontophoresis has not damaged the cells in spite of its significant effect on drug transport.

C) Stability Experiments:

The stability of the paracellular marker mannitol was investigated by passing a 100mV current through a 1mM solution of cold mannitol *via* Ag/AgCl electrodes. The sample was analysed for any degradative effects using Nuclear Magnetic Resonance (NMR) spectroscopy.

Nuclear Magnetic Resonance spectra of mannitol exposed to 100mV showed no signs of degradation in comparison with a control sample of mannitol. This is a key control experiment since it shows that the radiolabel cannot have detached from mannitol or that the flux was a fragment of the parent molecule: the increased flux on the basalateral side was intact radio labelled mannitol.

Example 3

TRH Permeability studies across rat colonic tissue under iontophoretic conditions

This example advances the principles set forth above as applied to test a tri-peptide. The effect of current (14.3μ-equivalents) on ^{3}H-TRH (0.1nM) absorptive flux enhancement was investigated using the experimental model described in Example 1, except that the duration of the test period was 30 min., in order for the required charge equivalents to be transferred.

The effect of 14.3 μ-equivalents charge (i.e. 750μA x 30min.) on the absorptive flux of thyrotropin releasing hormone (TRH) across rat colonic tissue was examined. The Papp values (cm/s) measured for each sampling period are outlined in Table 9 and Fig. 16.

Table 9

Papp (cm/s) value calculated for each interval in rat colon

Papp(cm/s) value for TRH calculated for each interval					
*Test voltage applied at 40-70 interval					
control (n=3)			14.3 μ-equiv. (n=4)		
interval	mean	sem	interval	mean	sem
0-20	1.94E-06	1.98E-07	0-20	2.44E-06	6.12E-07
20-40	3.96E-06	4.72E-07	20-40	5.15E-06	1.13E-06
40-70	5.28E-06	1.15E-06	*40-70	8.93E-06	6.04E-07
70-90	4.92E-06	1.00E-06	70-90	6.18E-06	8.44E-07
90-110	3.48E-06	1.22E-06	90-110	2.62E-06	7.55E-07

It will be observed that for the control experiments the TRH flux was linear across rat colon throughout the experiment. A significant increase (two fold) in TRH flux was seen due to the current application in the test period.

Transepithelial resistance (TEER) was stable with time as shown in Table 10 and Fig. 17.

Table 10

TEER measurements in rat colon

Transepithelial Resistance (Ohm.cm^2) measured at t=0,20,40,70,90,110 min.						
Test voltage applied at T=40 min.						
Expt:						
control (n=3)	t=0	t=20	t=40	t=60	t=80	t=100
mean	122.12	100.40	90.55	78.47	89.28	104.29
sem	3.94	4.47	14.06	13.30	14.92	22.05
14.3μ-equiv. (n=4)						
mean	92.21	65.63	60.68	66.59	73.14	78.43
sem	18.00	12.28	13.96	18.66	24.51	23.35

No effect on tissue integrity was noted after the current was applied. Basal short-circuit current, albeit quite low, was stable with time throughout the experiments and the results are shown in Table 11 and Fig. 18. Importantly, the short circuit current was similar in control and test tissue throughout.

Fig. 18 shows the short-circuit reading at the indicated times and the response to 3 and 10μM forskolin.

Table 11

Short-circuit current readings in rat colon

Expt:	Short-circuit current measured at:							
control (n=3)	t=0	t=20	t=40	t=60	t=80	t=100	3μM FSK	10μM FSK
mean	4.67	2.00	0.83	0.33	1.33	0.50	26.50	51.00
sem	1.48	0.50	0.17	1.01	0.44	0.29	3.91	4.19
14.3μ-equiv. (n=4)								
mean	6.75	4.88	3.25	1.38	1.50	1.75	22.63	38.13
sem	3.48	1.89	0.66	0.47	1.02	0.97	2.63	6.59

Forskolin response (10μM) in test tissue was significantly lower although a mean of 38μA is still a high effect and proves that the tissue is behaving in a functional synctium.

The charge equivalents being transferred across the epithelium in these experiments were calculated and are illustrated in Table 12 and Fig. 19.

Table 12

Charge (μ-equivalents) transferred across rat colon

Charge (μ-equivalents) transferred across epithelium calculated for each experiment					
Tissue under open circuit except for test period (*40-70)					
TEST:					
control	t=0-20	t=20-40	t=40-70	t=70-90	t=90-110
mean	1.47E-03	1.84E-03	2.73E-03	2.14E-03	1.88E-03
sem	9.82E-04	1.31E-03	1.57E-03	1.48E-03	1.41E-03
14.3μ-equiv.					
mean	2.90E-03	2.71E+03	1.43E+01	7.12E-03	2.29E-03
sem	6.79E-04	7.90E-04	8.17E-02	5.40E-03	6.09E-04

It will be appreciated that the embodiments discussed above are preferred embodiments, falling within the scope of the appended claims, and that various alternative embodiments are contemplated.

Claims: -

1. A device for delivering an agent across the intestinal wall of a mammal comprising:

means for applying a potential across the intestinal wall of a mammal;

agent; and

means for locating the agent proximate to the intestinal wall.

2. A device according to Claim 1, wherein the means for applying a potential comprises a pair of electrodes and a power source.

3. A device according to Claim 2, wherein the electrodes are made of Ag/AgCl.

4. A device according to Claim 2, wherein the electrodes are made of carbon.

5. A device according to Claim 2, wherein the electrodes are made of platinum.

6. A device according to Claim 2, wherein the electrodes are made of stainless steel.

7. A device according to any one of Claims 2 to 6, wherein the electrodes comprise a swellable polymer.

8. A device according to Claim 7, wherein the swellable polymer is selected from polyvinyl pyrrolidones, polyethylene imines, polyacrylic acids and alginates.

9. A device according to any one of Claims 2 to 8, wherein the power source comprises a battery.

10. A device according to Claim 9, wherein the battery is a polymer-based solid state miniature battery.

11. A device according to any preceding claim, wherein the means for locating the agent comprises a swellable polymer.

12. A device according to any preceding claim, wherein the applied potential generates a current that enables the agent to be delivered across the intestinal wall *via* iontophoresis.

13. A device according to any preceding claim, wherein the intestinal wall comprises the intestinal mucosa.

14. A device according to any preceding claim, which is delivered orally.

15. A device according to any one of Claims 1-13, wherein the device is delivered rectally.

16. A device according to any preceding claim, wherein the means for locating the agent proximate to the intestinal wall is actuated by a substance found in the gastrointestinal tract.

17. A device according to any preceding claim, wherein the agent is embedded in the locating means.

18. A device according to any preceding claim, wherein the locating means is covered by a pH-sensitive coating adapted to delay the actuation of the locating means until after the device has left the stomach and entered the small intestine.

19. A device according to any one of Claims 1-17, wherein the device is coated by a pH-sensitive coating which is soluble in the environment of the intestine.

20. A device according to Claim 19, wherein the device is coated by a pH-sensitive coating which is soluble in the environment of the small intestine.

21. A device according to Claim 20, wherein the device is coated by a pH-sensitive coating which is insoluble in the environment of the stomach.

22. A device according to Claim 19, wherein the device is coated by a pH-sensitive coating which is soluble in the environment of the large intestine.

23. A device according to Claim 22, wherein the device is coated by a pH-sensitive coating which is soluble in the environment of the rectum.

24. A device according to any one of Claims 18-23, wherein the pH-sensitive coating comprises a polymer selected from cellulose acetate trimellititate, hydroxypropylmethylcellulose phthalate, polyvinyl acetate phthalate, cellulose acetate phthalate and polymers of acrylic acid and/or methacrylic acid and esters thereof.

25. A device according to Claim 11, wherein the swellable polymer swells upon contact with a liquid in the gastrointestinal tract.

26. A device according to any preceding claim, wherein the agent is coated with a charged material.

27. A device according to any preceding claim, wherein the agent is comprised of nanoparticles.

28. A device according to any preceding claim, wherein the agent is not readily chargeable.

29. A device according to any preceding claim, wherein the agent is normally susceptible to degradation in the gastrointestinal tract.

30. A device according to any preceding claim, further comprising means for controlling the rate at which potential is applied.

31. A device according to Claim 30, wherein the controlling means comprises an electronic control circuit.

32. A device according to any preceding claim, wherein the potential is in the range of 0.5-6.0 volts.

33. A device according to any preceding claim, wherein the agent is a protein.

34. A device according to any one of Claims 1-32, wherein the agent is a peptide.

35. A device according to any one of Claims 1-32, wherein the agent is selected from one or more of the following: hormones such as insulin, calcitonin, calcitonin gene regulating protein, atrial natriuretic protein, colony stimulating factor, betaseron, erythropoietin (EPO), interferons such as α, β or γ interferon, somatropin, somatotropin, somastostatin, insulin-like growth factor (somatomedins), luteinizing hormone releasing hormone (LHRH), tissue plasminogen activator (TPA), growth hormone releasing hormone (GHRH), thyrotropin releasing hormone (TRH), oxytocin, estradiol, growth hormones, leuprolide acetate, factor VIII, interleukins such as interleukin-2, and analogues thereof and immunosuppressants such as cyclosporines, and oral vaccines.

36. A device according to any one of Claims 1-16, wherein the agent contacts the intestinal wall.

37. A system for enhancing the delivery of an agent across the intestinal wall of a mammal comprising means for applying potential across the intestinal wall.

38. A system according to Claim 37, further comprising means for locating an agent proximate to the intestinal wall.

39. A system according to Claim 37 or 38, wherein the means for applying potential comprises a pair of electrodes and a power source.

40. A system according to any one of claims 37-39, wherein the means for applying potential generates a current that enhances delivery of an agent across the intestinal wall.

41. A system according to any one of Claims 37-40, wherein the intestinal wall comprises the intestinal mucosa.

42. A system according to any one of Claims 39-41, wherein the electrodes are made of Ag/AgCl.

43. A system according to any one of Claims 39-41, wherein the electrodes are made of carbon.

44. A system according to any one of Claims 39-41, wherein the electrodes are made of platinum.

45. A system according to any one of Claims 39-41, wherein the electrodes are made of stainless steel.

46. A system according any one of Claims 37-44, wherein the power source comprises a battery.

47. A system according to Claim 46, wherein the battery comprises a polymer-based solid state miniature battery.

48. A system according to any one of Claims 39-41, wherein the electrodes comprise a swellable polymer.

49. A system according to Claim 48, wherein the swellable polymer is selected from polyvinyl pyrrolidones, polyethylene imines, polyacrylic acids and alginates.

50. A system according to any one of Claims 37-49, further comprising means for controlling the means for applying potential.

51. A system according to Claim 50, wherein the controlling means comprises an electronic control circuit.

52. A system according to any one of Claims 37-51, wherein the agent is a protein.

53. A system according to any one of Claims 37-51, wherein the agent is a peptide.

54. A system according to any one of Claims 37-51, wherein the agent is selected from one or more of the following: hormones such as insulin, calcitonin, calcitonin gene regulating protein, atrial natriuretic protein, colony stimulating factor, betaseron, erythropoietin (EPO), interferons such as α, β or γ interferon, somatropin, somatotropin, somastostatin, insulin-like growth factor (somatomedins), luteinizing hormone releasing hormone (LHRH), tissue plasminogen activator (TPA), growth hormone releasing hormone (GHRH), thyrotropin releasing hormone (TRH), oxytocin, estradiol, growth hormones, leuprolide acetate, factor VIII, interleukins such as interleukin-2, and analogues thereof and immunosuppressants such as cyclosporines, and oral vaccines.

55. A system according to any one of Claims 37-54, wherein the potential is in the range of 0.5-6.0 volts.

56. A system according to any one of Claims 37-55, wherein the system is ingested orally.

57. A system according to any one of Claims 37-55, wherein the system is inserted into the rectum.

58. A means for delivering an agent across the intestinal wall of a mammal comprising:

means for locating an agent proximate to the intestinal wall; and

means for applying a potential across the intestinal wall of a mammal, whereby a current is generated across the intestinal wall, thereby opening the tight junctions of the intestinal epithelium to permit agent permeation.

59. A delivery means according to Claim 58, wherein the agent is a peptide.

60. A delivery means according to Claim 58 or 59, wherein the potential is in the range of 0.5-6.0 volts.

61. A delivery means according to any one of Claims 58-60, wherein the agent is a protein.

62. A delivery means according to any one of Claims 58-61, wherein the agent contacts the intestinal wall.

63. A method for delivering an agent across the intestinal wall of a mammal comprising the steps of:

locating an agent proximate to the intestinal wall; and

applying a potential across the intestinal wall of a mammal, whereby agent is delivered across the intestinal wall.

64. A method according to Claim 63, wherein the means for applying a potential comprises a pair of electrodes and power source.

65. A method according to Claim 63 or 64, wherein the means for locating the agent comprises a swellable polymer.

66. A method according to any one of Claims 63-65, wherein the application of potential generates a current that enables the agent to be delivered across the intestinal wall via iontophoresis.

67. A method according to any one of Claims 63-66, wherein the intestinal wall comprises the intestinal mucosa.

68. A method according to any one of Claims 63-67, wherein the electrodes are made of Ag/AgCl.

69. A method according to any one of Claims 63-67, wherein the electrodes are made of carbon.

70. A method according to any one of Claims 63-67, wherein the electrodes are made of stainless steel.

71. A method according to any one of Claims 63-67, wherein the electrodes are made of platinum.

72. A method according to any one of Claims 63-71, wherein the power source comprises a battery.

73. A method according to Claim 72, wherein the battery comprises a polymer-based solid state miniature battery.

74. A method according to any one of Claims 63-73, further comprising the first step of ingesting the locating and applying means orally.

75. A method according to any one of Claims 63-73, further comprising the first step of inserting the locating and applying means into the rectum.

76. A method according to any one of Claims 63-75, wherein the step of locating the agent proximate to the intestinal wall is actuated by a substance found in the gastrointestinal tract.

77. A method according to any one of Claims 63-76, wherein the agent is embedded in the locating means.

78. A method according to any one of Claims 63-77, wherein the locating means is covered by a pH-sensitive coating adapted to delay the actuation of the locating means.

79. A method according to Claim 78, wherein the pH-sensitive coating is soluble in the environment of the intestine.

80. A method according to Claim 78, wherein the pH-sensitive coating is soluble in the environment of the small intestine.

81. A method according to Claim 80, wherein the pH-sensitive coating is insoluble in the environment of the stomach.

82. A method according to Claim 78, wherein the pH-sensitive coating is soluble in the environment of the large intestine.

83. A method according to Claim 78, wherein the pH-sensitive coating is soluble in the environment of the rectum.

84. A method according to any one of Claims 78-83, wherein the pH-sensitive coating comprises a polymer selected from cellulose acetate trimellititate, hydroxypropylmethylcellulose phthalate, polyvinyl acetate phthalate, cellulose acetate phthalate and polymers of acrylic acid and/or methacrylic acid and esters thereof.

85. A method according to any one of Claims 65-84, wherein the swellable polymer swells upon contact with a liquid in the gastrointestinal tract.

86. A method according to any one of Claims 64-85, wherein the electrodes comprise a swellable polymer.

87. A method according to Claim 86, wherein the swellable polymer is selected from polyvinyl pyrrolidones, polyethylene imines, polyacrylic acids and alginates.

88. A method according to any one of Claims 63-87, wherein the agent is coated with a charged material.

89. A method according to any one of Claims 63-88, wherein the agent is comprised of nanoparticles.

90. A method according to any one of Claims 63-89, wherein the agent is not readily chargeable.

91. A method according to any one of Claims 63-90, wherein the agent is normally susceptible to degradation in the gastrointestinal tract.

92. A method according to any one of Claims 63-91, further comprising the step of controlling the rate at which potential is applied.

93. A method according to Claim 92, wherein the step of controlling the rate of potential application comprises the incorporation of an electronic control circuit.

94. A method according to any one of Claims 63-93, wherein the potential is in the range of 0.5-6.0 volts.

95. A method according to any one of Claims 63-94, wherein the agent is a peptide.

96. A method according to any one of Claims 63-94, wherein the agent is a protein.

97. A method according to any one of Claims 63-75, wherein the agent contacts the intestinal wall.

98. A method according to any one of Claims 63-97, wherein the step of applying a potential across the wall of the intestine comprises the steps of locating a pair of electrodes proximate to the wall and providing power to the electrodes so as to generate a current across the intestinal wall.

99. A method for delivering an agent across the intestinal wall of a mammal comprising the steps of:

locating an agent proximate to the intestinal wall; and

applying a potential across the intestinal wall of a mammal, whereby a current is generated across the intestinal wall, thereby opening the tight junctions of the intestinal epithelium to permit agent permeation.

100. A method according to Claim 99, wherein the agent is a peptide.

101. A method according to Claim 99 or 100, wherein the current is in the range of 5-200μA.

102. A method according to any one of Claims 99-101, wherein the agent is a protein.

103. A method according to any one of Claims 99-102, wherein the agent contacts the intestinal wall.

104. A method according to any one of Claims 99-103, wherein the step of applying a potential across the wall of the intestine comprises

the steps of locating a pair of electrodes proximate to the wall and providing power to the electrodes so as to generate a current across the intestinal wall.

105. A method of enhancing the delivery of an agent across the intestinal wall of a mammal comprising the step of applying a potential across the intestinal wall of a mammal.

106. A method according to Claim 105, further comprising the step of locating an agent proximate to the intestinal wall so that when potential is applied thereacross, delivery of the agent across the wall is enhanced.

107. A method according to Claim 105 or 106, wherein the step of applying potential comprises the step of applying a pair of electrodes in communication with a power source to the intestinal wall.

108. A method according to any one of Claims 105-107, wherein the applied potential is in the range of 0.5-6.0 volts.

109. A method according to any one of Claims 105-108, wherein the agent contacts the intestinal wall.

110. A method according to any one of Claims 105-109, further comprising the step of controlling the means for applying potential.

111. A device according to Claim 1 for delivering an agent across the intestinal wall of a mammal substantially as hereinbefore described with particular reference to and as illustrated in Figs. 1-4 of the accompanying drawings.

112. A system according to Claim 37 for enhancing the delivery of an agent across the intestinal wall of a mammal, substantially as hereinbefore described with particular reference to and as illustrated in Figs. 1-4 of the accompanying drawings.

113. A means according to Claim 58 for delivering an agent across the intestinal wall of a mammal, substantially as hereinbefore described with particular reference to and as illustrated in Figs. 1-4 of the accompanying drawings.

114. A method according to Claim 63 for delivery an agent across the intestinal wall of a mammal, substantially as hereinbefore described and exemplified.

115. A method according to Claim 99 for delivering an agent across the intestinal wall of a mammal, substantially as hereinbefore described and exemplified.

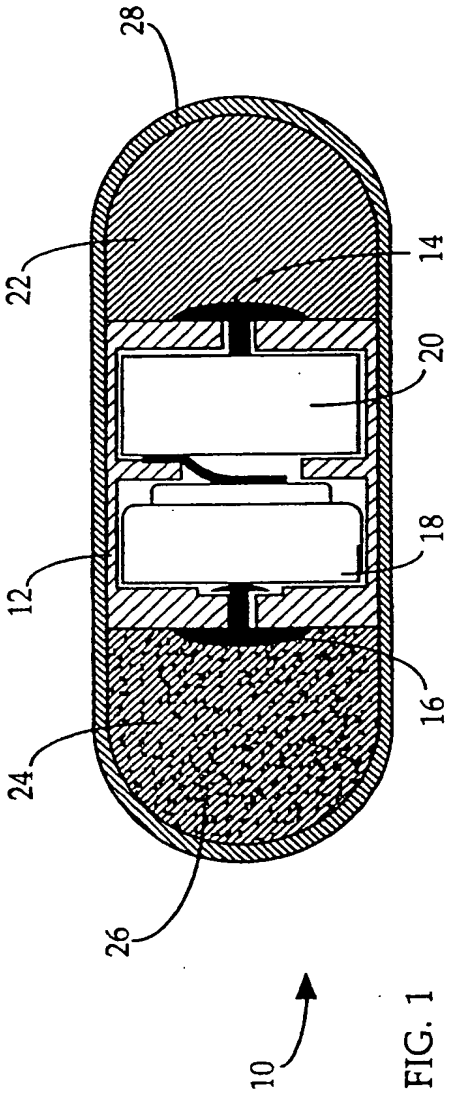


FIG. 1

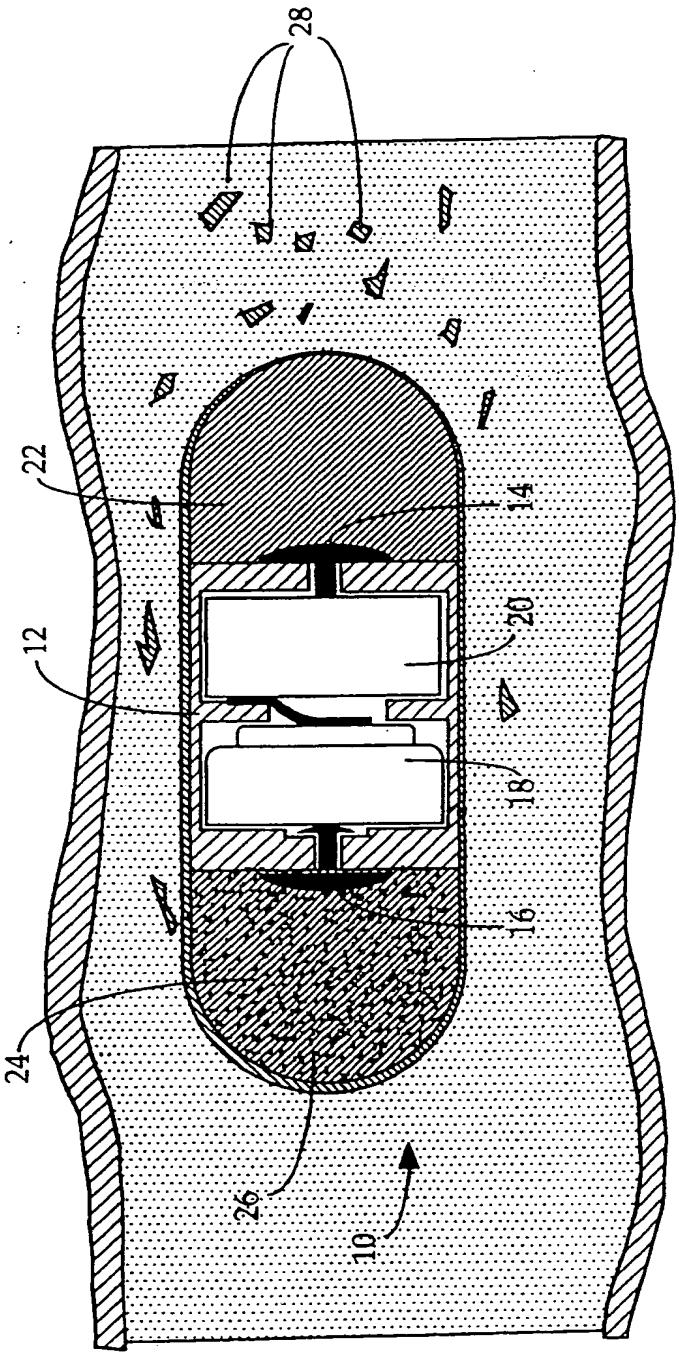


FIG. 2

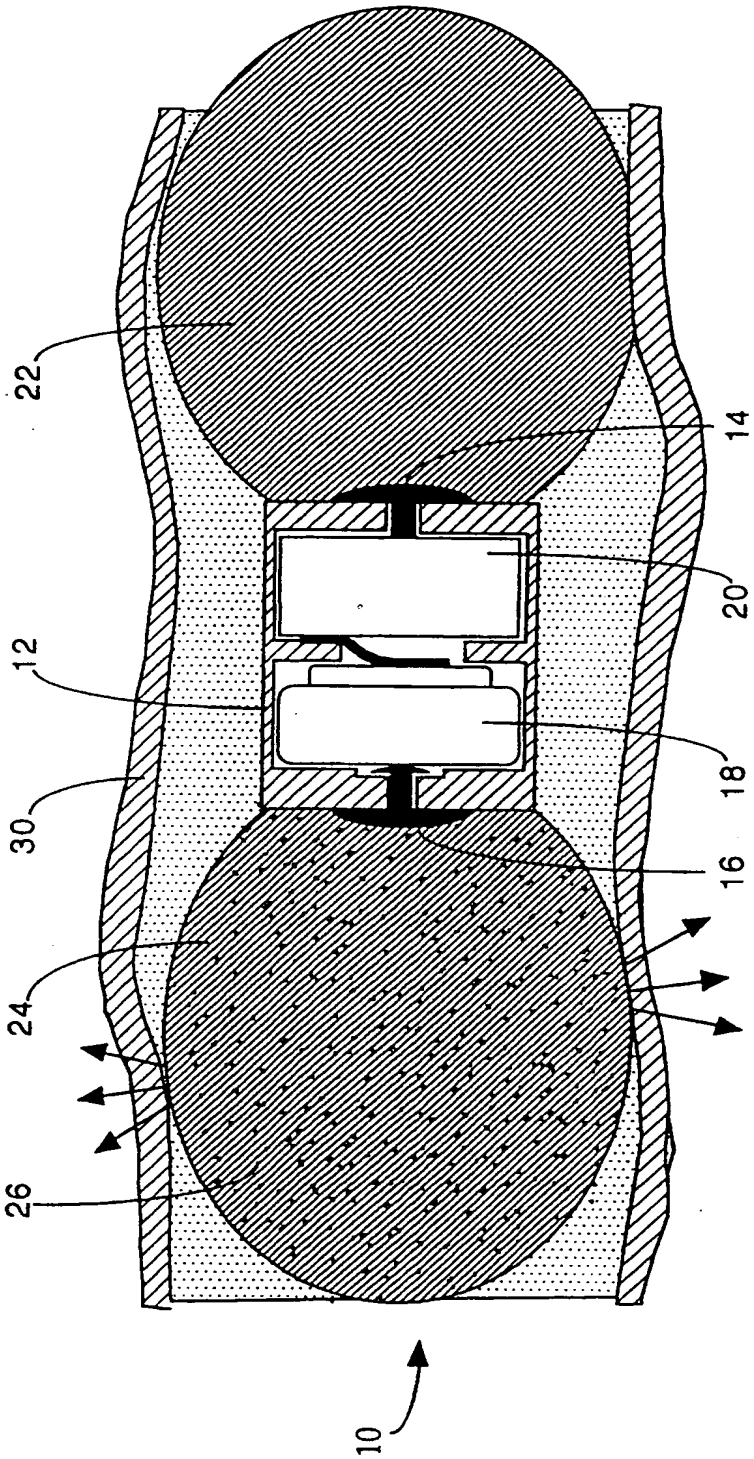


FIG. 3

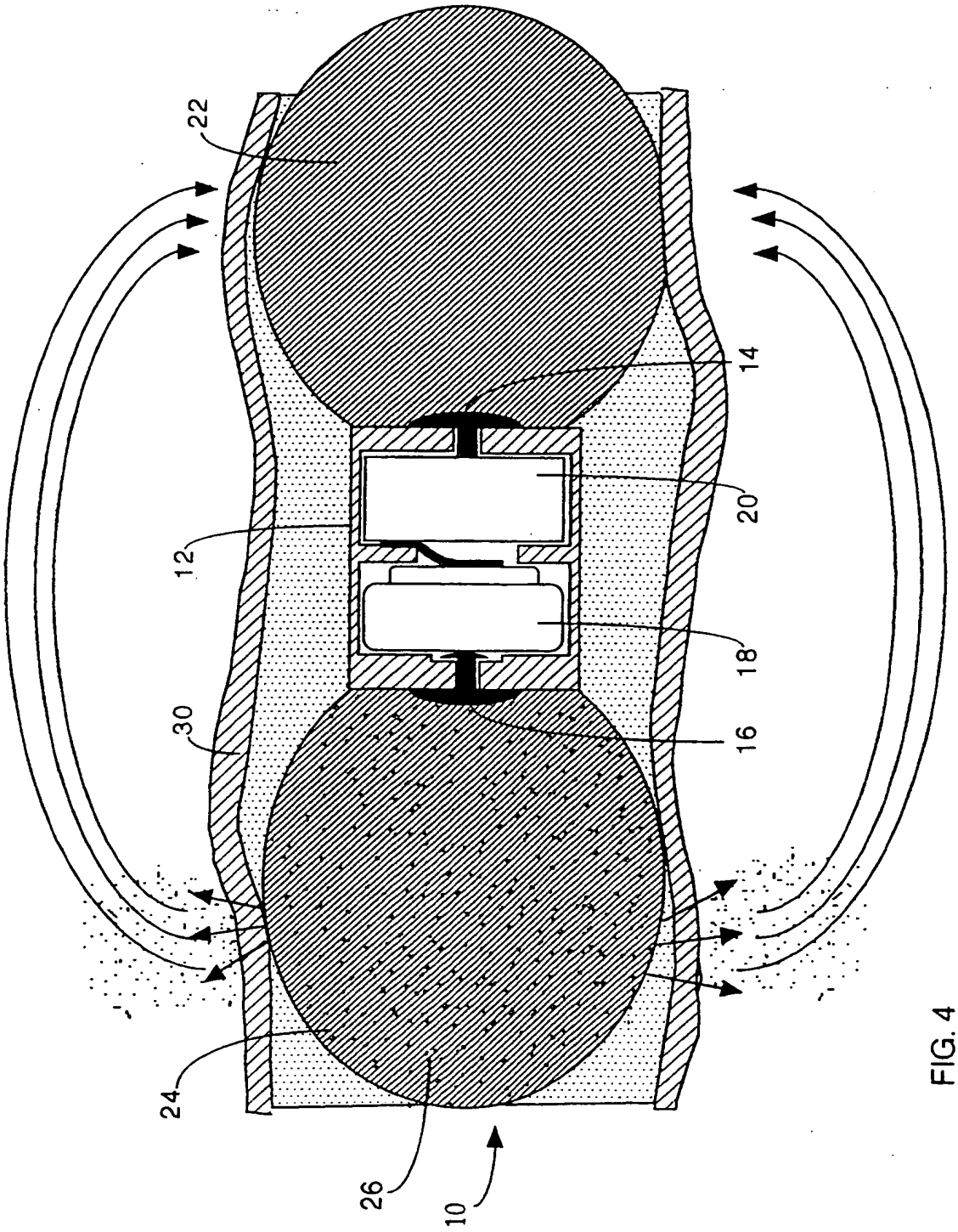


FIG. 4

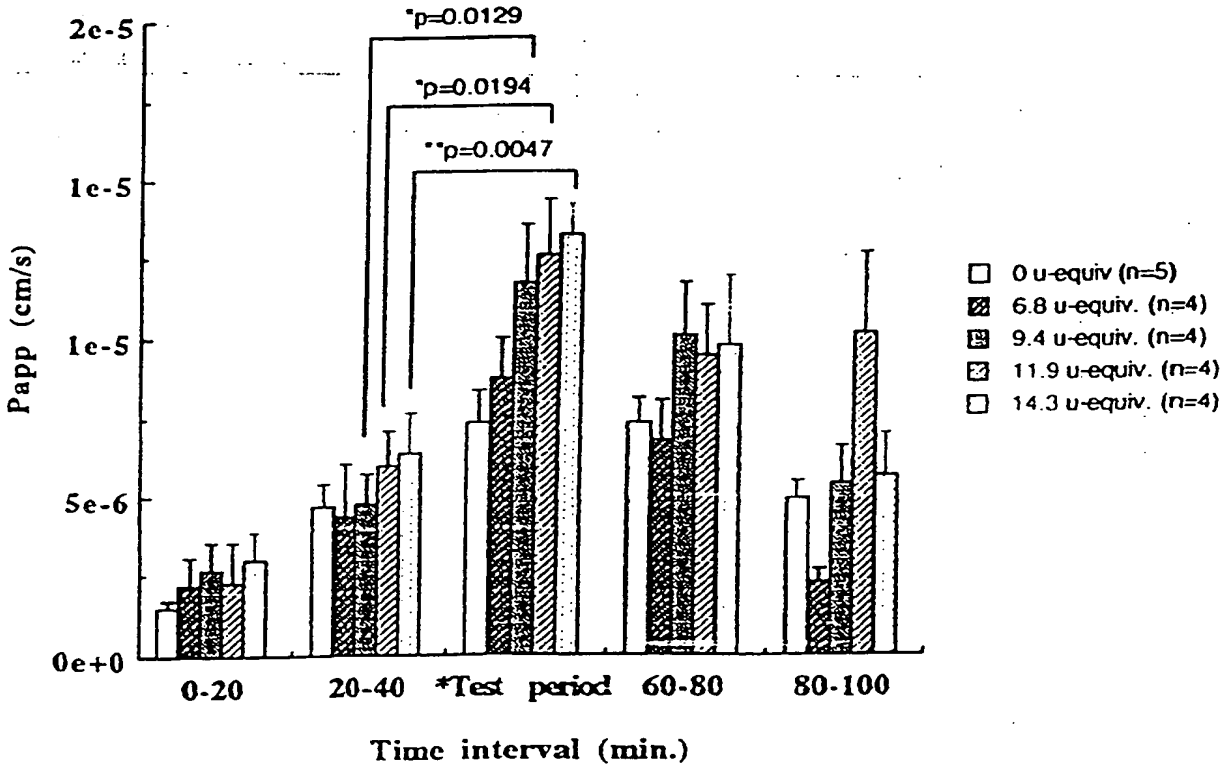

*p=0.0129
*p=0.0194
**p=0.0047
2e-5
1e-5
1e-5
5e-6
0e+0
Papp (cm/s)
0-20
20-40
*Test period
60-80
80-100
Time interval (min.)
0 u-equiv (n=5)
6.8 u-equiv. (n=4)
9.4 u-equiv. (n=4)
11.9 u-equiv. (n=4)
14.3 u-equiv. (n=4)

FIG. 5

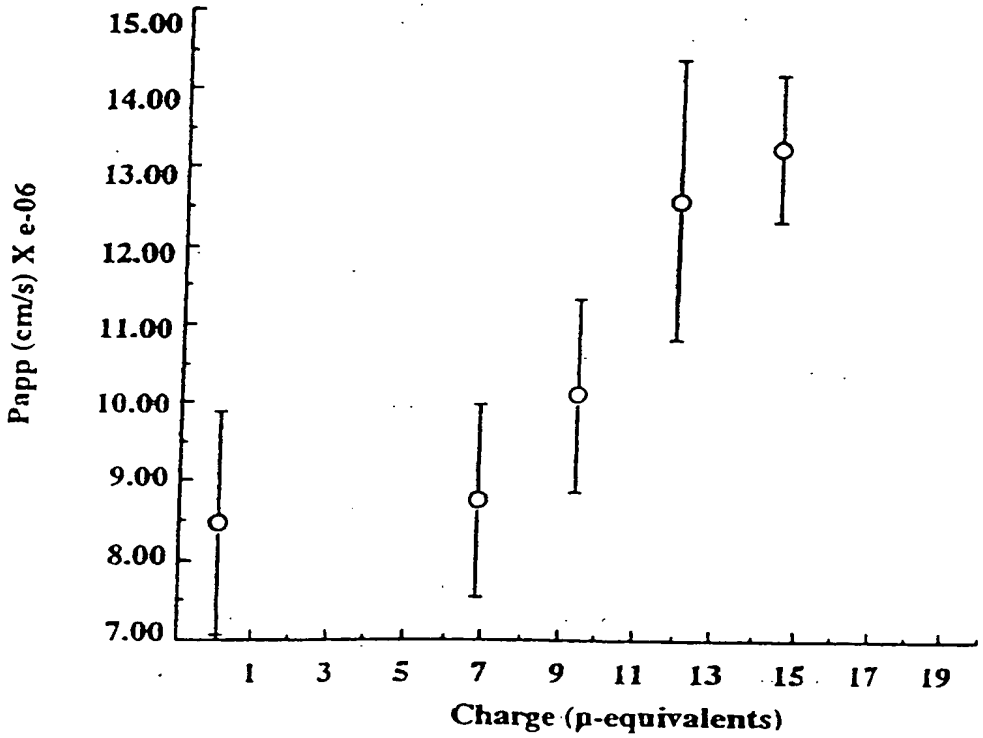


FIG. 6

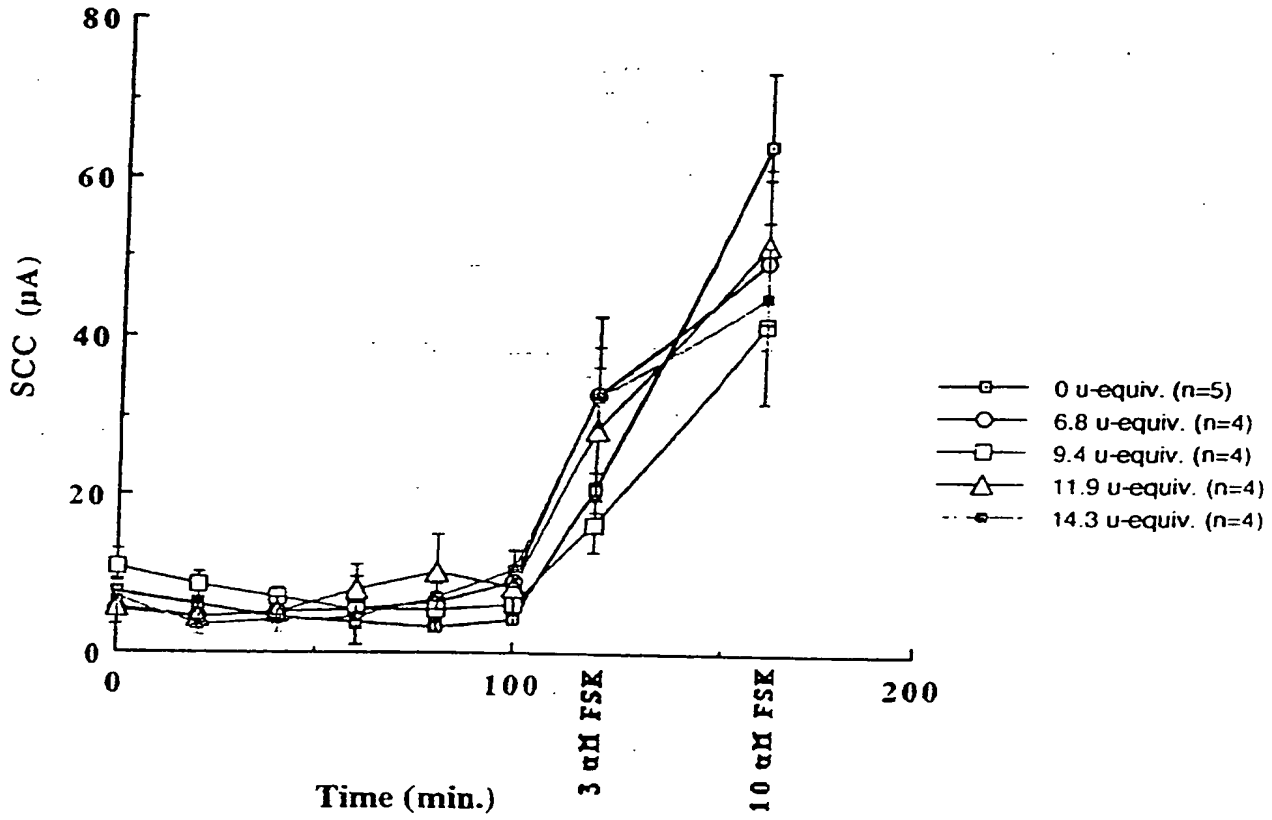


FIG. 7

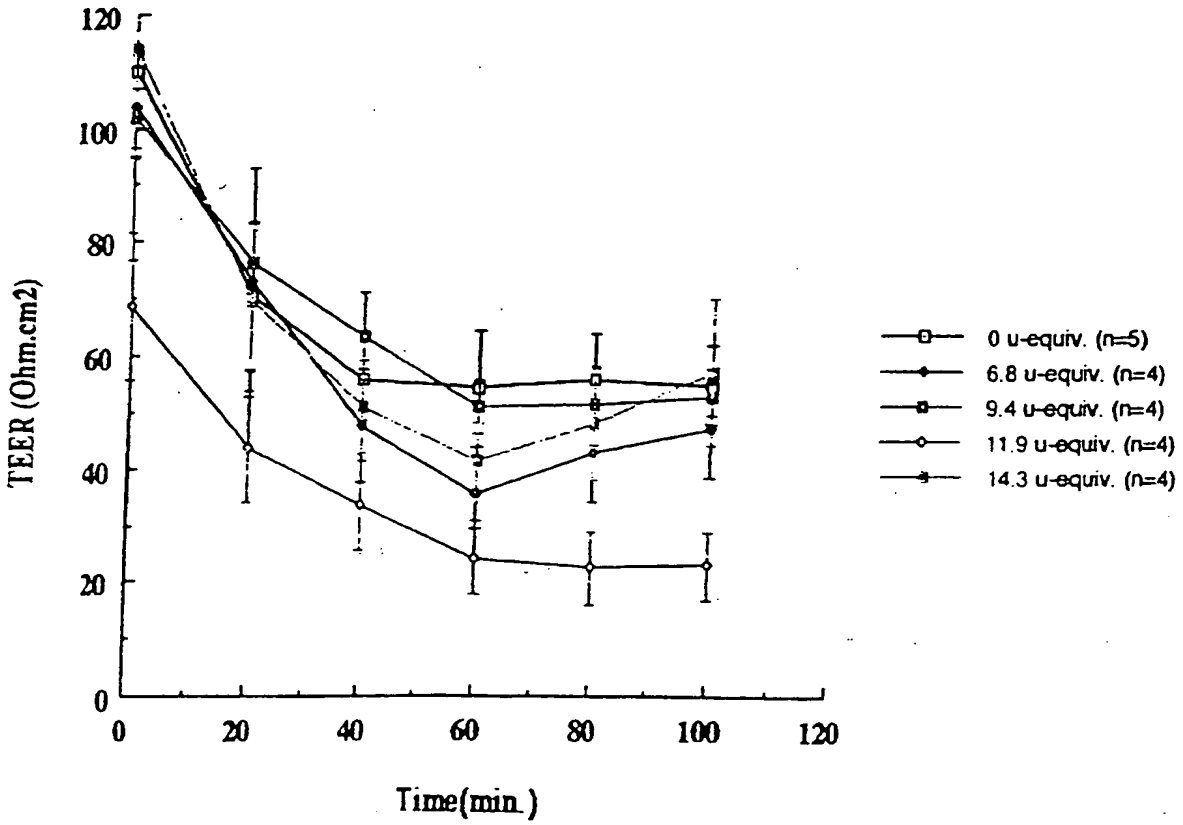

120
100
80
60
40
20
0
TEER (Ohm.cm2)
0
20
40
60
80
100
120
Time(min.)
0 u-equiv. (n=5)
6.8 u-equiv. (n=4)
9.4 u-equiv. (n=4)
11.9 u-equiv. (n=4)
14.3 u-equiv. (n=4)

FIG. 8

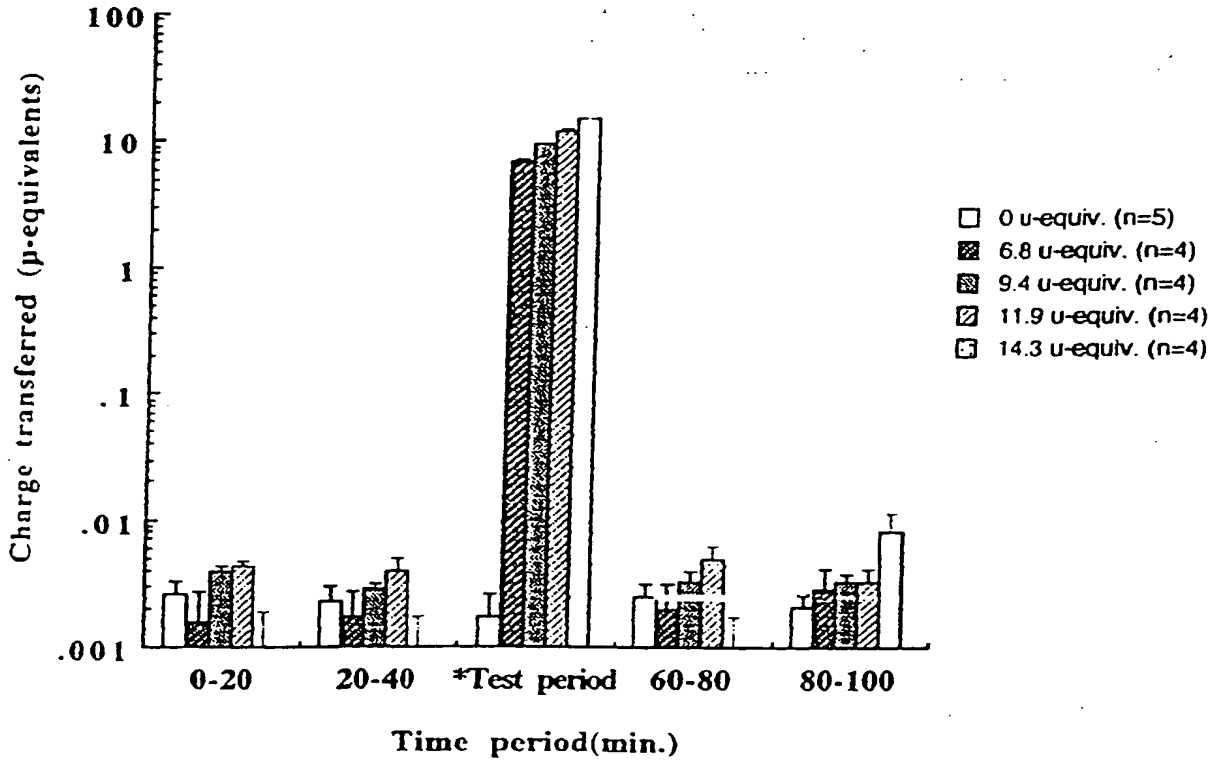
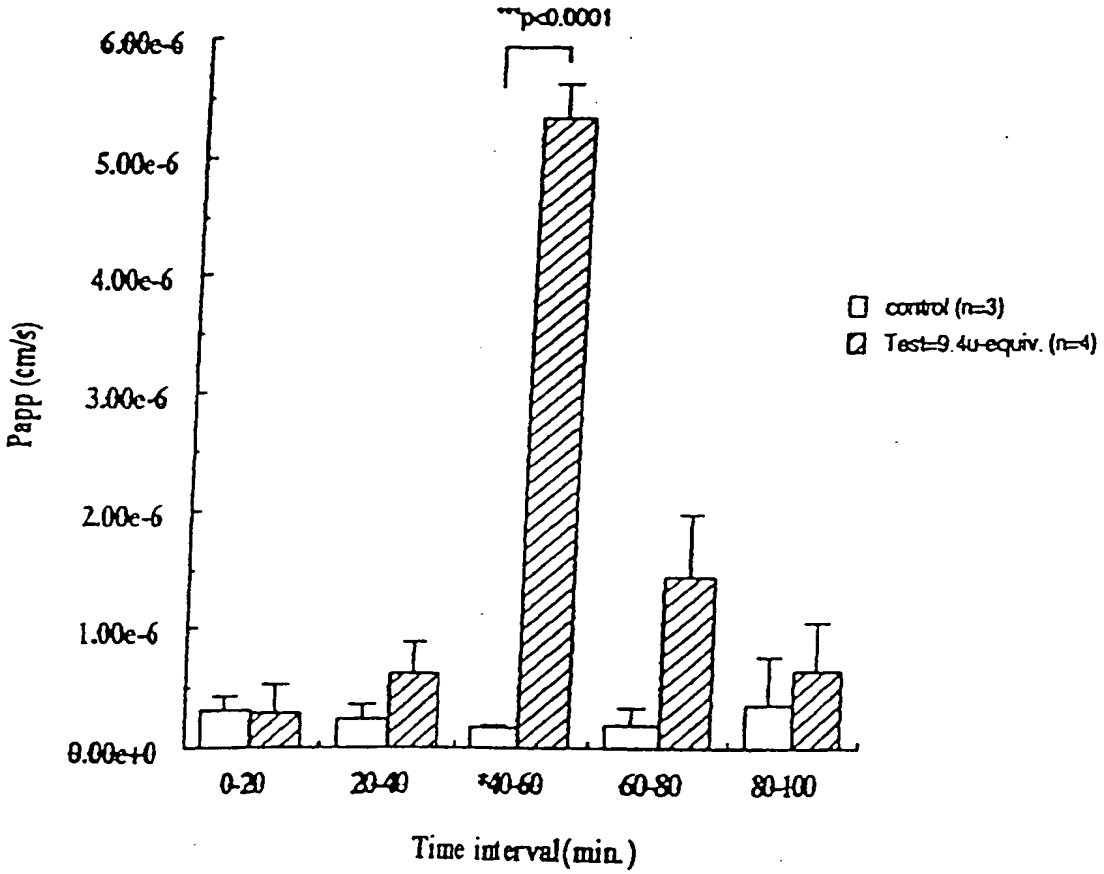


FIG. 9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6.00e-6
5.00e-6
4.00e-6
3.00e-6
2.00e-6
1.00e-6
0.00e+0
Papp (cm/s)
0-20
20-40
*40-60
60-80
80-100
Time interval(min.)
control (n=3)
Test=9.4u-equiv. (n=4)

FIG. 10

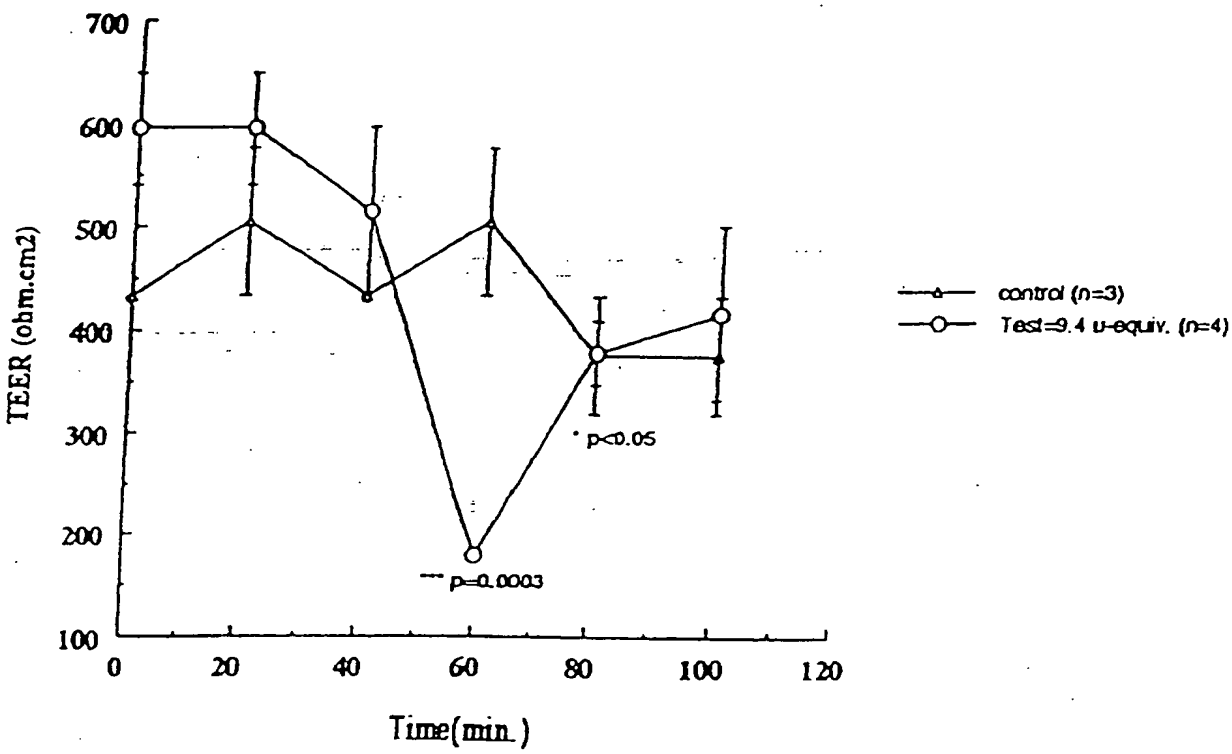

FIG. 11

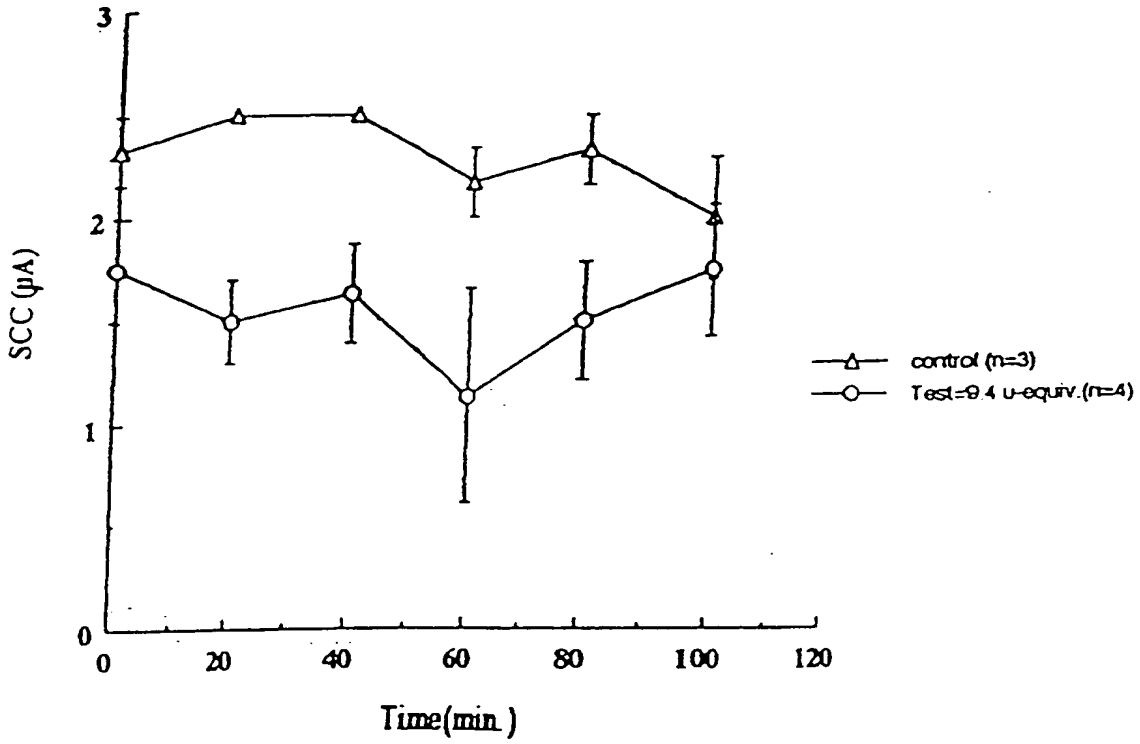

FIG. 12

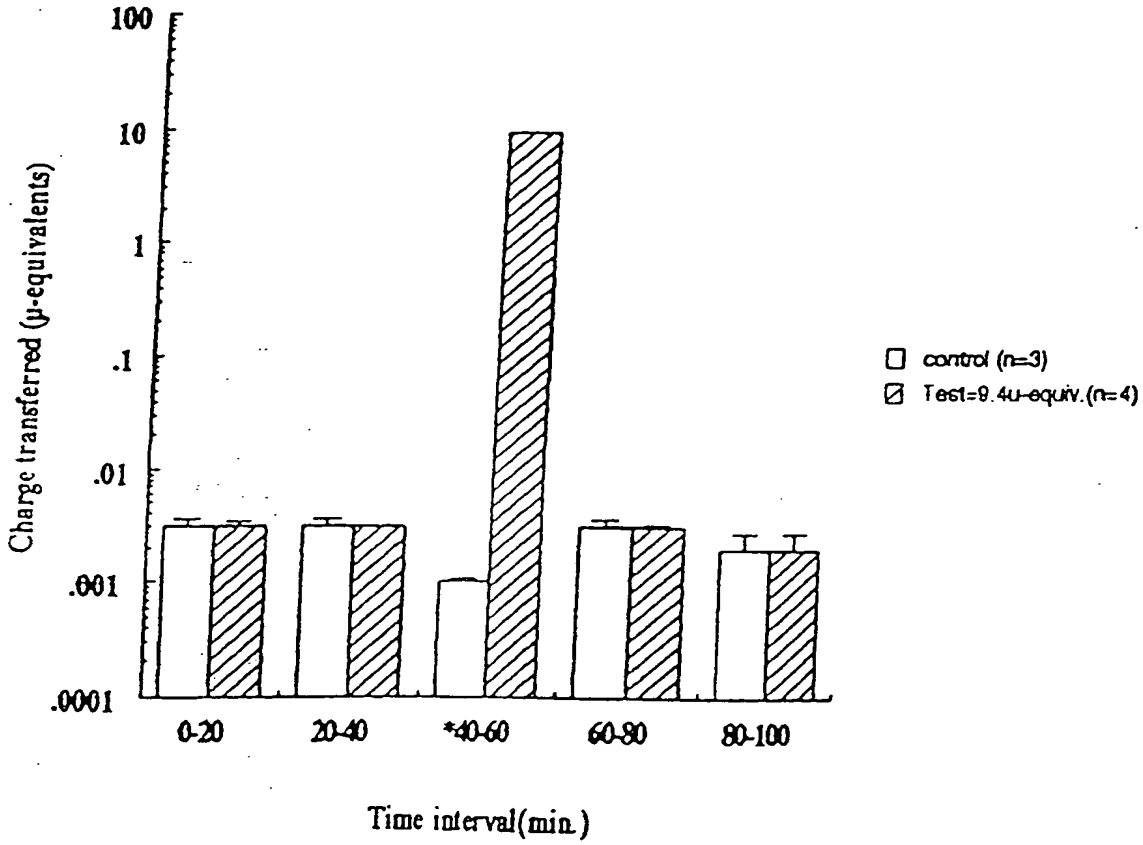

FIG. 13

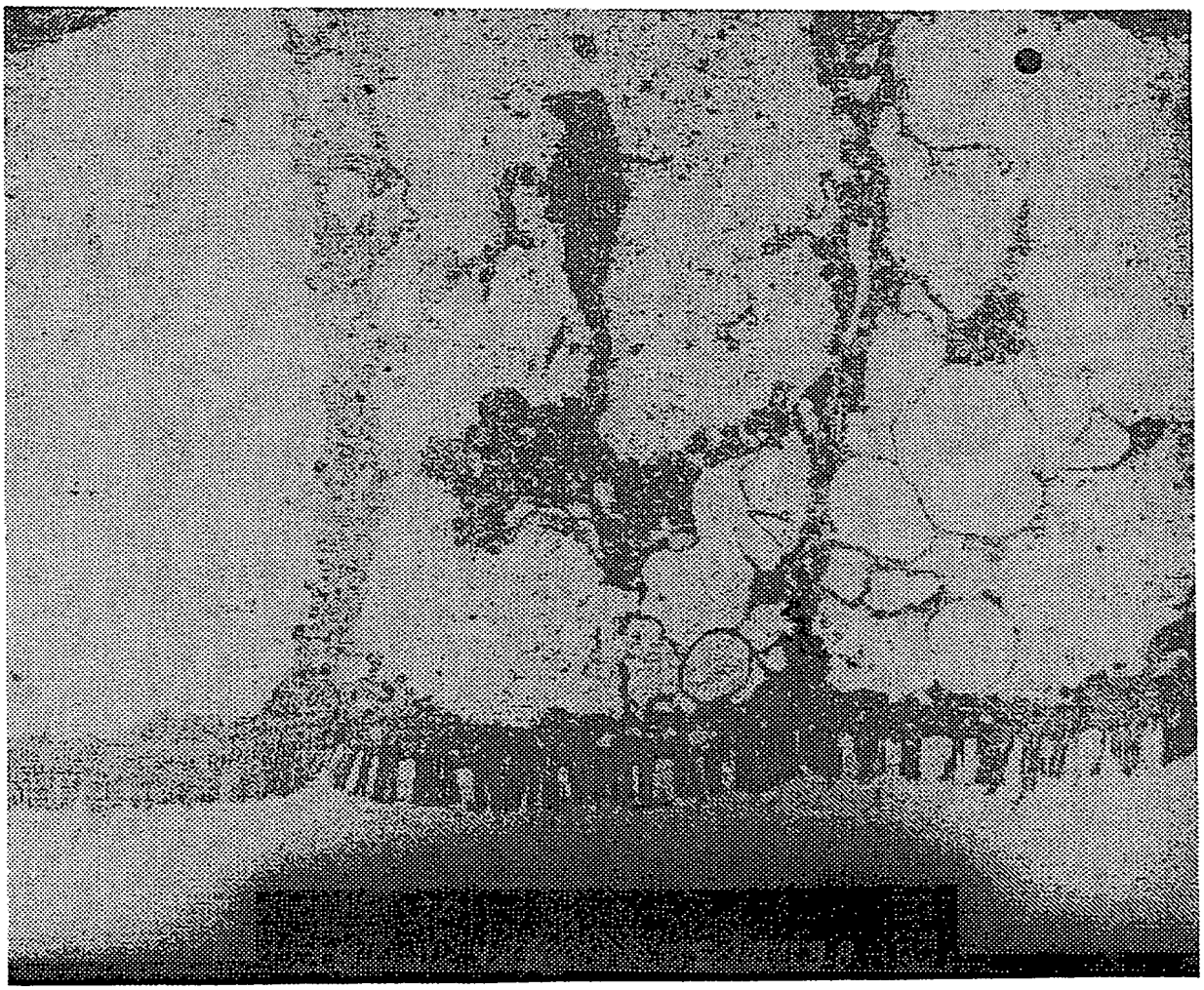

FIG. 14

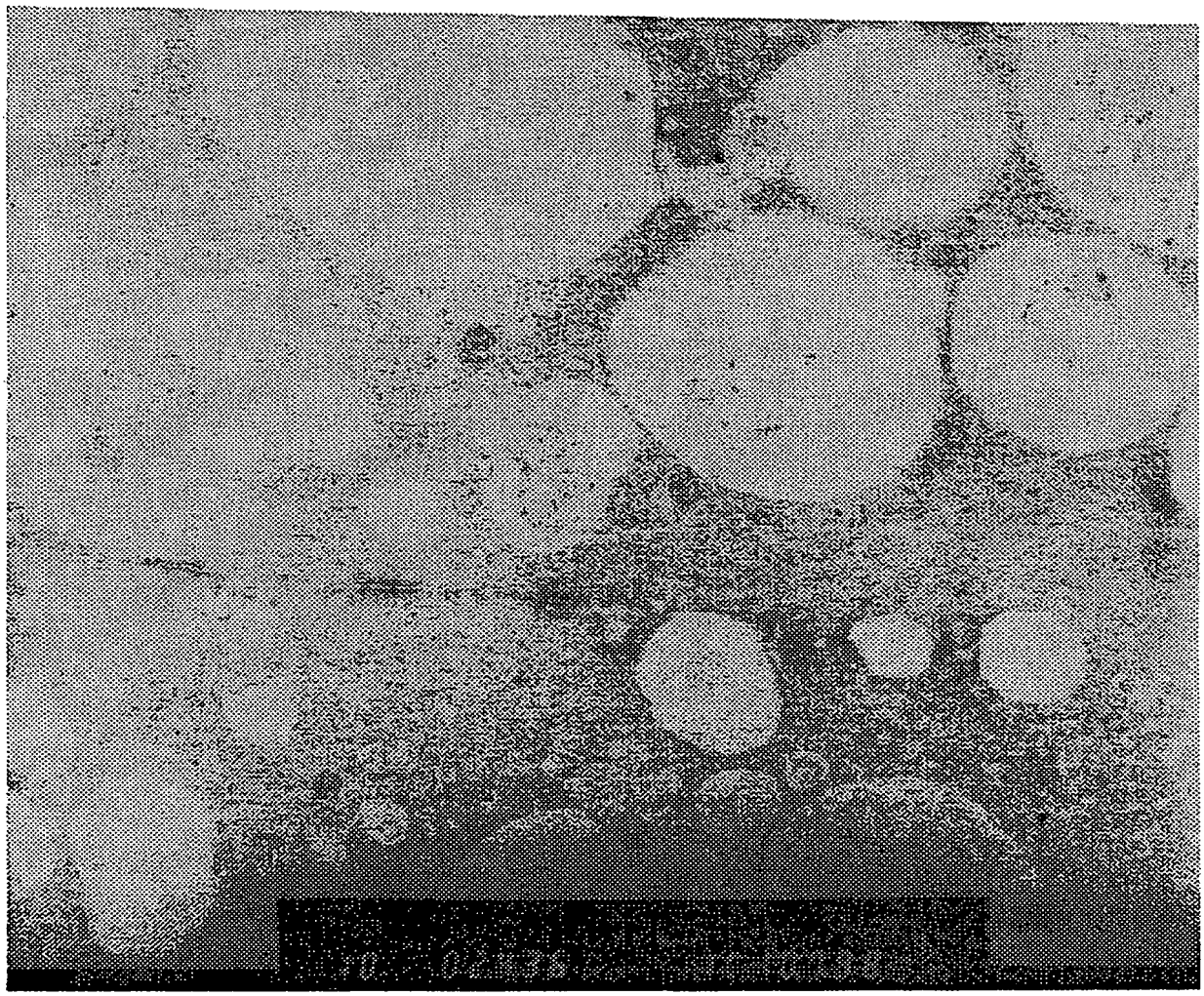

FIG. 15

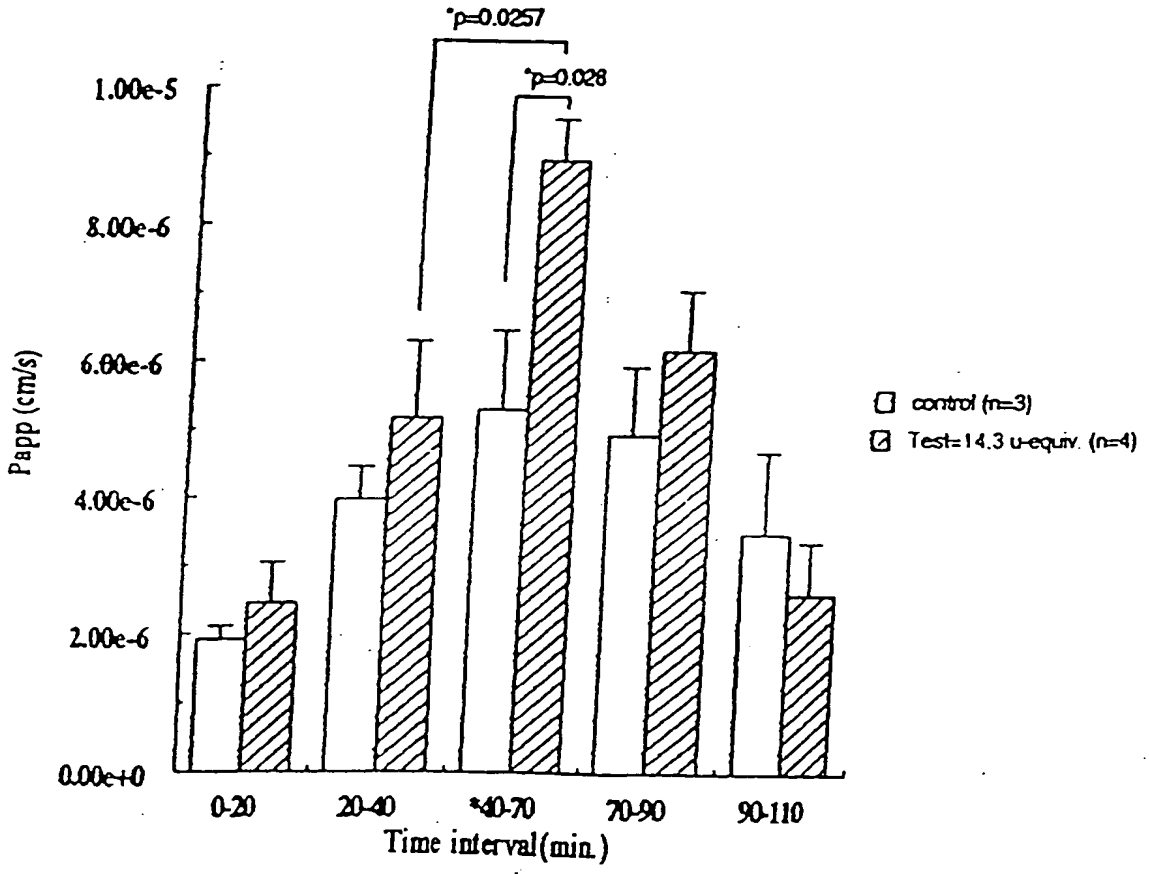

FIG. 16

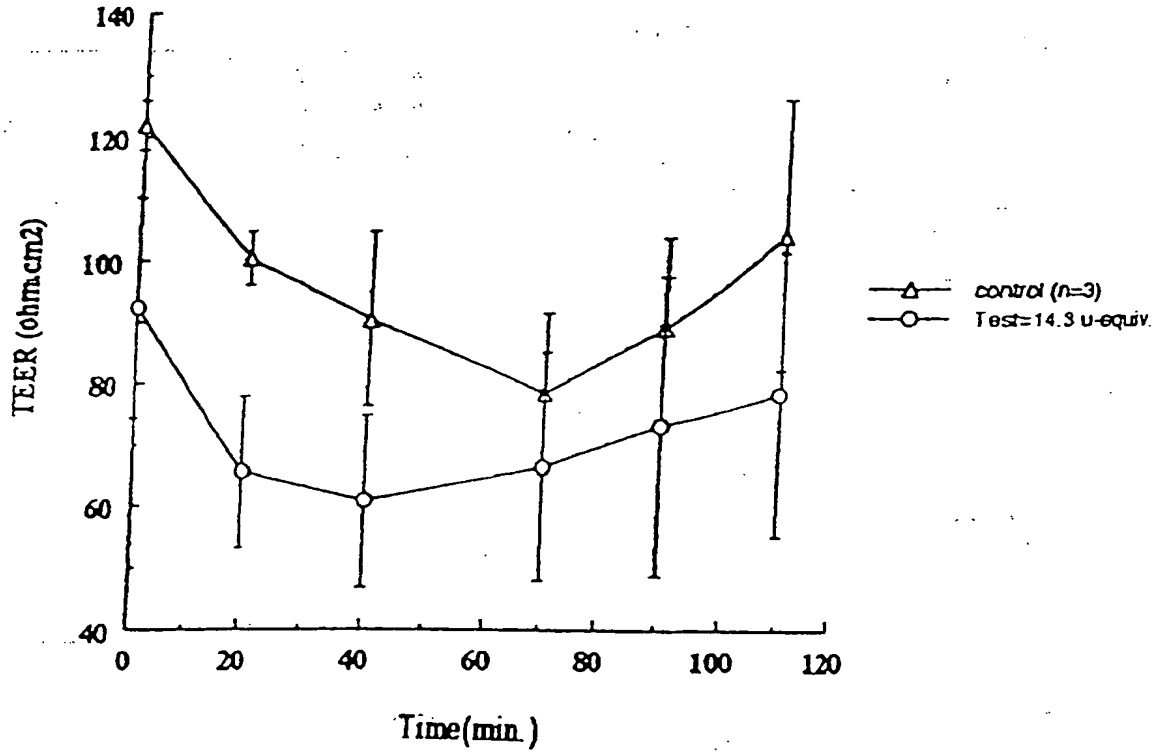

FIG. 17

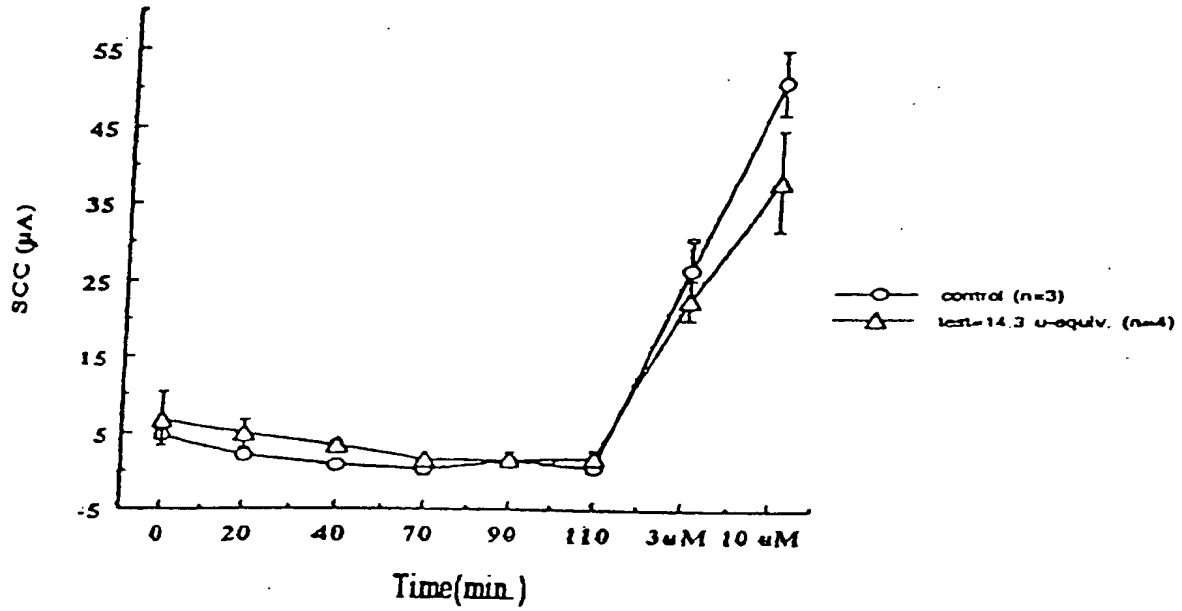

FIG. 18

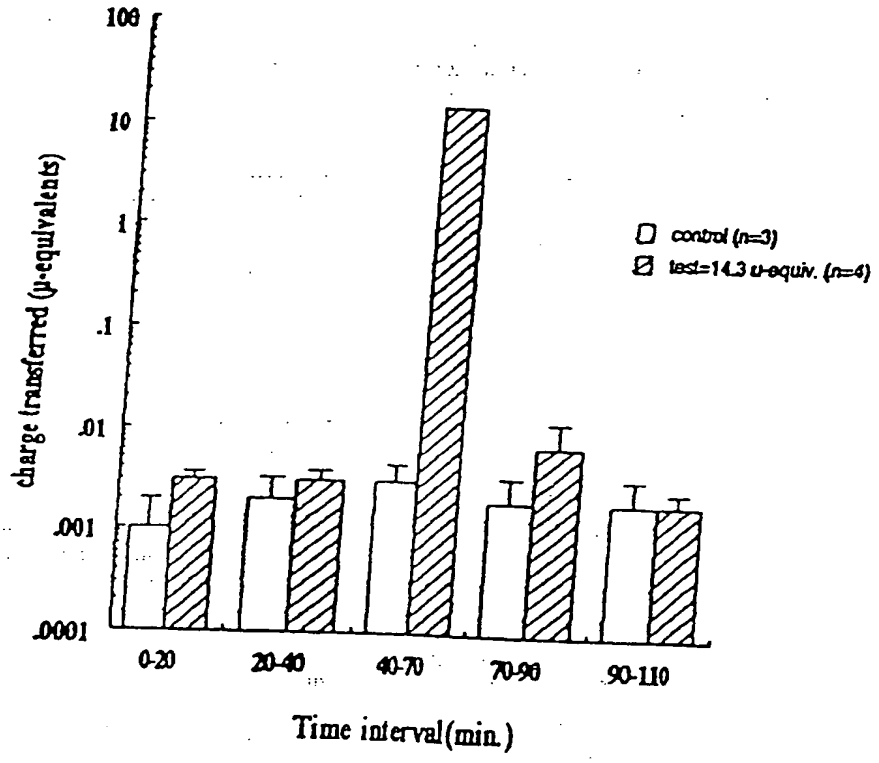
100
10
1
.1
.01
.001
.0001
charge transferred (μ-equivalents)
control (n=3)
test=14.3 u-equiv. (n=6)
0-20
20-40
40-70
70-90
90-110
Time interval(min.)

FIG. 19

INTERNATIONAL SEARCH REPORT

Int. .tional Application No
PCT/IE 99/00097

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/00 A61N1/30

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K A61N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category '	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 282 785 A (SHIMADA JIN ET AL) 1 February 1994 (1994-02-01) column 2, line 10 -column 4, line 44 claim 1; figure 1; example --- -/--	1,2, 12-15, 28,30, 36-41, 50, 56-58, 62-64, 66,67, 75,90, 92,97, 99,103, 105,106, 109-115

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

' Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 December 1999	22/12/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl. Fax: (+31-70) 340-3016	Epskamp, S

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Int. ational Application No
PCT/IE 99/00097

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication.where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97 36644 A (IOTEK INC) 9 October 1997 (1997-10-09) page 4, line 13 -page 5, line 8; figure 1 page 9, line 7 -page 10, line 12; figure 7	1,2,7,9, 11-15, 17,30, 36-41, 46,48, 50, 56-58, 62, 111-113

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IE 99/00097

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 63-110 and 114-115 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

information on patent family members

Inte ional Application No
PCT/IE 99/00097

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5282785 A	01-02-1994	US 5286254 A	15-02-1994
		AT 123658 T	15-06-1995
		AU 8074591 A	07-01-1992
		DE 69110467 D	20-07-1995
		DE 69110467 T	01-02-1996
		EP 0533816 A	31-03-1993
		WO 9119529 A	26-12-1991
		US 5498238 A	12-03-1996
		US 5499971 A	19-03-1996
		US 5628730 A	13-05-1994
		US 5458568 A	17-10-1995
		AU 3321293 A	29-03-1994
		AU 3321793 A	29-03-1994
		EP 0611311 A	24-08-1994
		JP 7500523 T	19-01-1995
		WO 9405361 A	17-03-1994
		WO 9405369 A	17-03-1994
WO 9736644 A	09-10-1997	US 5816248 A	06-10-1998